



**PHD**

**The cortical origins of rheumatology pain**

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# The Cortical Origins of Rheumatology Pain

Submitted by: Candida S. McCabe MSc RGN

For the degree of PhD  
of the University of Bath  
2004

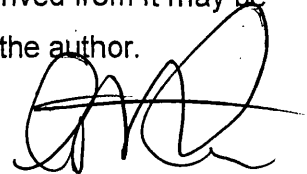
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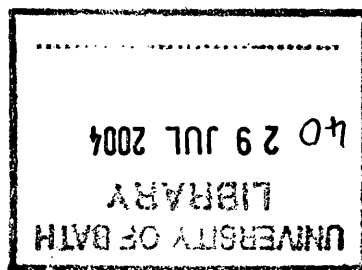
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# The Cortical Origins of Rheumatology Pain

*"It is inherently ridiculous to consider pain as an isolated entity although many do exactly that. Our understanding brains steadily combine all available information from the outside world and from within our bodies... our personal ...and our genetic histories. The outcomes are decisions of the tactics and strategies which could be appropriate to respond to the situation. We use the word pain as shorthand for one of these groupings of relevant response tactics and strategies"*

Patrick Wall, 1999

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## Summary

Pain is the predominant complaint of those with a rheumatological condition. In the majority of cases clinical findings provide supporting evidence for the source of this pain. However, there are some conditions in rheumatology where a patient's pain cannot be matched to physical findings or relieved by traditional therapeutic measures. It is pain of this nature that this thesis explores.

A review of the current theories on the mechanisms of pain, will show that the experience of pain may derive from both peripheral and central mechanisms (at the spinal and cortical level), and that pain may continue after the original injury has healed. Complex Regional Pain Syndrome (CRPS) will then be focused upon, as this condition has evidence of both peripheral and central mechanism involvement, which may arise without major neural trauma. A review of the presenting symptoms, treatments and current theories on the pathophysiology of this disease will illustrate the complexity of this condition.

Clinical findings, which suggest cortical sensory reorganisation in CRPS are illustrated and discussed. It is proposed that this sensory reorganisation generates pain and altered body image in these patients, in the same manner, as has previously been hypothesised for amputees with PLP. This is via a motor/sensory conflict within the motor control system. The correction of this conflict through the provision of appropriate visual sensory input, using a mirror, is tested in a population of patients with CRPS. Its analgesic efficacy is assessed in those with acute, intermediate and chronic disease. Finally, the hypothesis is taken to its natural conclusion whereby motor/sensory conflict is artificially generated in healthy volunteers, to establish whether sensory disturbances can be created where no current symptoms of pain exist.

The findings of my studies support the hypothesis that a mismatch between motor output and sensory input creates sensory disturbances, including pain, in rheumatology patients and healthy volunteers. I propose the term *ominory* to describe the central monitoring mechanism, and the resultant sensory disturbances, as a *dissensory state*.



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### **Thanks**

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## **Glossary of terms**

Allodynia	Experience of pain induced by a stimulus which does not normally produce pain.
Dysaesthesia	An unpleasant abnormal sensation which may be spontaneous or evoked.
Dystonia	Muscular spasm resulting in abnormal posture.
Hyperaesthesia	Excessively sensitive to non-noxious stimuli.
Hyperalgesia	An increased response to stimulus which is normally painful.
Hyperhidrosis	Excessive sweating
Hypohidrosis	Reduced sweating
Hyperpathia	A painful syndrome, characterised by increased reaction to a stimulus as well as an increased threshold.

## **OUTLINE OF THESIS**

Pain is the predominant complaint of patients with a rheumatological condition. It may be intermittent or continuous and vary in nature depending on the cause and course of the disease. In the majority of cases clinical findings provide supporting evidence for the source of this pain, such as swollen joints in Rheumatoid arthritis or bony overgrowth in Osteoarthritis. However, there are some conditions in rheumatology where a patient's pain cannot be matched to physical findings or relieved by traditional therapeutic measures. It is pain of this nature that this thesis explores.

The primary condition of interest is Complex Regional Pain Syndrome Type 1 (CRPS) and the reader will see how the multifaceted nature of this disease and its close similarities with amputee phantom limb pain, ideally lends itself to exploring how peripheral and central mechanisms relate to each other in the generation of pain. It will be shown that greater knowledge in this field can lead to the development of novel therapeutic techniques and new theories on how pain and other sensory disturbances are generated in otherwise healthy individuals. Greater understanding of pain mechanisms can only enhance the management and treatment of those in pain, and the identification of those at risk of developing it.

### **Over arching hypothesis:**

'Pain, in some rheumatic diseases, is cortical in origin'

### **Structure of thesis**

This thesis is divided into three sections. Each chapter addresses a separate area of study which builds upon the knowledge gained in the previous chapter. The first section comprises review papers of current pain theories and complex regional pain syndrome (Chapters one and two). Chapters four to six describe three discrete research studies with separate hypotheses, aims, methods, results and discussion sections. The first study seeks evidence of cortical changes in CRPS to underpin a recent proposed model of pain based on sensorimotor disruption. The second and third test this model; firstly in

CRPS, using a novel therapeutic technique and secondly, on healthy volunteers, to establish if pain and other sensory disturbances can be generated. The findings from all three research studies will be drawn together in the final section, Chapter seven, where the implications of this work will be fully discussed. Where commonalities in methodology do exist these have been presented in Chapter three, prior to the research studies, to reduce repetition.

# CHAPTER ONE

## **Pain mechanisms and the rheumatic diseases**

(Appendix 1; McCabe, 2004 *in press*)

### **1.1 Introduction**

Pain is a familiar sensation to us all, whether it is the sharp pain from a cut, the sting of a nettle or the nagging ache of a tooth. For the majority of us our experience of pain is in unconnected, resolvable incidents that are interspersed by lengthy pain free periods. However, for those with a rheumatic disease their pain may be ever present. The character and intensity of that pain may vary depending on the cause and course of their disease and even be influenced by diurnal patterns.

Traditionally we associate pain with injury, but the chronic pain of conditions such as fibromyalgia tests this belief, and patients and clinicians alike may find it hard to understand how pain can apparently strike from nowhere. This chapter will provide a broad overview of the current theories on the mechanisms of pain and how these may relate to the seemingly incomprehensible symptoms of pain and other sensory disturbances that Rheumatology patients' experience

### **1.2 What do we mean by pain?**

The word pain is derived from the Latin word 'poena' meaning penalty, and some people still believe that the pain they or others experience is due to some real or imagined misdemeanour. Pain is not a sensation that is ever felt alone; its emotional effects always accompany it. It is usually a negative experience involving both physical and mental processes, but may serve as a survival mechanism whereby minor pain may ensure withdrawal from a potentially life threatening scenario, or enforce inactivity to ensure we take time to rest and heal (Melzack and Wall, 1996a).

The relationship between pain and injury is not always as expected. Melzack and Wall (1996b) describe how, although the severity of an injury

usually determines the intensity of the pain, there are instances where an injury may be sustained but pain not experienced until some time later. Conversely, severe pain may be experienced in the absence of tissue damage or long after an injury has apparently healed. The complexity of the experience has taxed scientists in defining it, with the focus in recent years primarily on tissue damage that produces the sensation of 'hurt' (Sternbach, 1968, Mountcastle, 1980). This then raises the questions of "How do you define 'hurt'?" and "What about pain that occurs in the absence of tissue damage?" The International Association for the Study of Pain defined pain as:

'An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.' (Merskey et al., 1979)

This was the first definition that recognised the emotional dimension of pain and that injury and pain may not always be linked. It also demonstrates that pain is a subjective event which relies on the sufferer 'describing' the experience. This acknowledgement that both physical and mental processes are involved has fuelled the search for a mechanism that creates a sensation from a sensory input, and then interprets that message using our mental processes (Wall, 1999a). A single mechanism or pain centre has proved elusive, and our understanding of this complex system is still far from complete.

### **1.3 Pain mechanisms –past to present**

The traditional explanation for our perception of pain is based on the 'specificity theory' that was first described in 1664 by Descartes (Melzack and Wall, 1996c). Descartes proposed that a specific pain system conveys messages from pain receptors in the skin to the brain, using a system rather like a bell at the end of a rope. The rope is pulled, i.e. the skin is damaged, the message goes down the 'rope' and the bell is rung, i.e. the brain is alerted.

This simple theory remained relatively unchanged until the nineteenth century when greater knowledge of anatomy and physiology began to emerge. What became apparent at this time was that the 'specificity theory' did not allow for all the other associated sensations that combine to give you an experience

of pain. Descartes had not allowed for the psychological contribution of pain, such as the effect of past experience or the current situation. The scientists of the nineteenth century, namely Muller and von Frey (Boring, 1942), contributed greatly to our understanding of the physiological mechanism of pain, but again no allowance was made for any psychological modulation of it. Muller recognised that it is the sensory nerves that are instrumental in the transmission of external information to the brain, and von Frey described specific sensory spots on the skin that recognise touch, cold, warmth and pain.

It was not until after 1965, following the publication of Ronald Melzack and Patrick Wall's Gate Control Theory of pain (Melzack & Wall, 1965), that pain theories started to encompass the influence of psychological factors (Melzack and Casey, 1968). These theories succeeded in combining the existing knowledge of pain into a clear and concise theory on the nature of the experience of pain.

In order to fully understand Melzack and Wall's (1965) seminal work, and how subsequent theories have built upon it, a brief review of the nervous system and its associated structures will be covered.

#### **1.4 How do pain messages travel?**

Sensory experiences are determined by a combination of the capacity of our nervous system to extract information from the stimuli that our bodies receive, and the ability to process that neural input (Doubell et al., 1999). Our peripheral sensory nerves comprising, A $\beta$  (fast, myelinated), A $\delta$  (thinly myelinated) and C-fibres (slow, unmyelinated), perform the task of data gathering by transmitting information from the peripheries to the central nervous system. These highly specialised structures each transmit a unique signal to enable identification and differentiation of the stimuli. The A $\delta$ - and C-fibres are thought to be primarily responsible for the transmission of impulses associated with pain. The fast A $\delta$ -fibres transmit the sharp pain of an acute injury, and the slower C-fibres produce the dull, aching pain of a deeper, more persistent injury, and the burning quality of neuropathic pain. The sensations experienced when an ankle is sprained typify the subtle differences of these two types of fibres. Initially a sharp, precisely localised pain is experienced which rises

rapidly in intensity but then falls away equally quickly ( $A\delta$ -fibres). After this, a second, quite different pain is felt; it is deep, diffuse, poorly localised, steady and spreading (C-fibres).

The first stage of information processing occurs at the dorsal horn in the spinal cord where these afferent sensory nerves terminate. Here, information from the peripheries is interpreted and acted on through interaction with the central nervous system (CNS). It is here that the Gate Control Theory of pain comes into play.

### **1.5 Gate Control Theory of Pain (Fig. 1)**

When small diameter  $A\delta$ - and C fibres are stimulated following injury, impulses are sent direct to the dorsal horn of the spinal cord where neurons, or transmission cells (T), are stimulated. These T-cells transmit information to the local reflex circuits and the brain, but will be suppressed when there is increased activity of large  $A\beta$ -fibres. In addition to the T-cells there are also small cells in the substantia gelatinosa (SG) which have an inhibitory effect on the deeper dorsal horn neurones. Small fibre activity will suppress this inhibitory effect and large fibre activity excites it. This results in an accentuated effect on T-cell activity so that when small fibres are active, T-cells are stimulated and the SG is suppressed, so that the 'gate opens' and messages pass to the brain to be perceived as pain. Conversely when large fibres become active, they excite the inhibitor of the SG and suppress T-cell activity, thereby closing the gate (Melzack and Wall, 1996d). This explains why one's immediate instinct following injury is to rub the affected area as  $A\beta$ -fibres transmit the sensation of touch and, therefore, increased activity of these large fibres will decrease pain. Acupuncture and transcutaneous electrical nerve stimulation (TENS) are targeted to work on the same principle, through the excitation of large fibre activity.

Nerve impulses that descend from the brain further influence this spinal gating system. Large-diameter, rapidly conducting fibres activate selective cognitive processes, which in turn, by way of descending fibres, modulate the properties of the spinal gating system. When the output of the T-cells in the



dorsal horn exceeds a critical level the action system is activated. This action system is what initiates the complex patterns of behaviour and experience that give rise to the distinctive nature of pain (Melzack and Wall, 1965). Exactly which areas of the brain are involved is the source of much debate, and it could be argued that virtually all of the brain plays a role in the experience of pain, such is the complexity of the emotional and physical response. However, the brain stem, medulla, pons and midbrain are thought to be key players (Wall 1999a), and these areas in turn receive information from the cord and the forebrain. The limbic system (comprising hypothalamus, hippocampus, amygdala, septum and cingulum) and the reticular formation, sited in the midbrain, are considered to be particularly important for the behavioural and emotional responses to pain, with the somatosensory cortex locating the site of the injury (Melzack and Wall 1996e).

Endogenous narcotics, such as endorphins and enkephalins, are produced in the forebrain and midbrain. These also modulate the transmission of pain signals in the dorsal horn via the descending pathway. Serotonin is the major transmitter for these opioid-like substances and, along with noradrenaline, it will trigger the release of these substances from spinal cord cells (Melzack and Wall, 1996e). Drugs such as Fluoxetine and Amitriptyline, used for depression and some forms of pain, work by suppressing the re-uptake of these transmitters, thereby prolonging their action.

Whereas Descartes' theory proposes that people respond to pain by a simple cause and effect mechanism, we now understand that psychological processes, accessed via the descending pathway, modulate this effect. This modulation by cognitive processes explains to some extent, how pain is more than a single sensation. It is an experience, and one that may alter depending on an individual's previous and current life events.

Fig 1 Schematic diagram of the Gate control theory of pain.

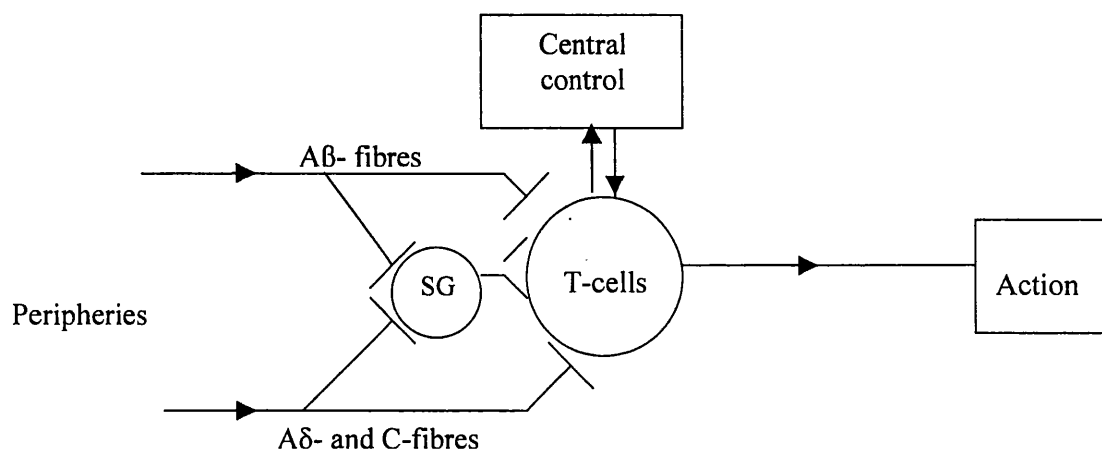


Figure 1. Large ( $A\beta$ - fibres) and small diameter fibres project to the Transmission cells (T-cells) and substantia gelatinosa (SG) in the dorsal horn of the spinal cord from the peripheries. The large fibres inhibit T-cell activity and the small fibres excite it. The inhibitory effect of the SG is increased by large fibre activity and suppressed by small fibre activity. Descending large diameter fibres from central mechanisms modulate this gate-control system and influence the resulting action.

## 1.6 Peripheral and central sensitisation

The Gate Theory of pain focuses primarily on how the CNS processes sensory information, and it is portrayed as a somewhat hard-wired system. However, we now know that this is not the case. Neural circuits can reconfigure in response to external and/or internal stimuli. The acknowledgement that neural plasticity occurs is one of the major developments in current pain theory, and its effect on the type and experience of pain may be significant. A persistent pain in the peripheries (such as chronic inflammation) can alter both peripheral and central signalling mechanisms.

Tissue damage incurred when you sprain your ankle will result in a cascade of activities, as chemicals are discharged into the area that surrounds the nerve endings. Mast cells will release chemicals such as bradykinin, histamine and prostaglandins, which either produce pain themselves or sensitise the nerve endings. The prostaglandins are particularly important as they dilate the blood vessels and make them leaky, resulting in the typical redness and swelling of injury (Melzack and Wall, 1996f). The mode of action of aspirin is to reduce the build up of prostaglandins.

The high thresholds of both A $\delta$ - and C-fibres ensure that they are normally only triggered by noxious stimuli. However, this threshold can be lowered when persistent stimuli occur, and these nociceptors (sensory receptors that react to painful stimuli) will start to fire on weak, non-noxious stimuli (Devor and Seltzer, 1999). This sensitisation occurs in the peripheries (primary hyperalgesia) due to the release of chemical inflammatory mediators (e.g. substance P) into the skin from damaged C fibres, or as outlined above via tissue damage. Nerve fibres may also begin to fire spontaneously, so that painful sensations are perceived even without stimulus. In addition, sensitisation may occur centrally if nociceptor inputs persist (secondary hyperalgesia). With persistent stimulus from damaged tissue and nerves there is an increase in the activity of calcium channels within the spinal cord. These affect both pre-synaptic transmitter release and post-synaptic neuronal excitability (Dickenson, 2002). The drug Gabapentin is a calcium antagonist and is therefore particularly appropriate for neuropathic pain. Active calcium channels increase the release

of glutamate, which is the key transmitter for afferent A- and C-fibres, and consequently increased activity of glutamate receptors (e.g. N-methyl-D-aspartate [NMDA]) that are implicated in wind-up and central sensitisation (Dickenson, 1995). The findings of allodynia (pain due to normally innocuous stimuli) and hyperalgesia (increased response to normally painful stimuli) may be seen on clinical examination, as this sensitisation can result in a lowering of the A $\beta$  fibres threshold so that touch now becomes a painful sensation.

In summary, when central sensitisation occurs, peripheral sensory neurone activity drives the central spinal systems and these in turn increase and prolong the incoming messages, so that, ultimately, a disassociation occurs between the peripheral activity and the individual's experience of pain (Dickenson, 2002). This explains the apparent anomaly that when a nerve is cut pain is not reduced or stopped, but actually exacerbated. A progressively damaged, hard-wired system would decrease in function, but these are dynamic systems that fluctuate as circumstances change (Wall, 2000). Central and peripheral sensitisation are thought to serve as protective mechanisms, with the increase in pain ensuring that behaviour is adapted to limit further damage (Devor and Seltzer, 1999).

### **1.7 Cortical remapping**

With the advent of sophisticated imaging techniques, objective evidence of neural plasticity at the cortical level has been widely reported in some chronic pain conditions (Ramachandran, 1993, Byl and Melnick, 1997, Elbert et al, 1998). These studies have shown changes on the somatosensory map following either an increase in sensory input, such as from the repetitive arm movements of professional musicians, or a decrease e.g deafferentation after limb amputation. Cortical areas that previously processed information from only one region, have been shown to encroach on adjacent areas of the somatosensory map. For example, upper limb amputees were found to have sensory input from the face and upper arm invading the hand territory of the somatosensory cortex (Ramachandran, 1993). Clinical evidence of this remapping is evident in the observation of referred sensations in amputees (Ramachandran et al., 1992). That is when somatosensory feelings are perceived to emanate from a body part other than, but in association with, the

body part being stimulated. We will see in Chapter four that these have also been found in patients with Complex Regional Pain Syndrome (McCabe et al., 2003a), thereby supporting the hypothesis that central mechanisms play a part in this chronic pain condition.

Recent thinking suggests that these cortical changes may not merely be a result of chronic pain, but instrumental in the generation of it (Harris, 1999). Harris (1999) hypothesised that if there is conflict between motor intention, proprioception and vision, then pain may be generated in the same manner that the sensation of nausea is generated when vision and vestibular sensory inputs conflict in sea sickness. An example of this would be amputee phantom limb pain, where motor output still perceives the limb to be present, but proprioceptive and visual input is absent from the amputated area.

The role of the motor control system is to manage the relationship between motor commands and sensory feedback (Frith et al., 2000). This is to optimise the precision and efficacy of a movement, as every movement results in an immediate sensory response. However, it is impossible to predict a sensory response purely from the motor commands, and so the system relies on information known as 'state variables' (Frith et al., 2000). These include such things as joint angles and the current state of the system prior to the command being implemented. From an assimilation of this information the motor control system 'predicts' a certain response from the sensory system, and 'controllers' within the system compare this desired state with the motor command required to achieve that state. The controllers then produce the appropriate motor commands to achieve the desired outcome. The prediction, or 'efference' copy, is often only a rough approximation of the actual consequences of a motor command, but it is needed to prepare the system for the consequences of that movement, assess performance if there is a delay in response, differentiate between internal and external influences on the system, and maintain a constant update on the interplay between sensory and motor systems. This prediction is then compared to that of actual sensory feedback, and the current state of the system modified accordingly (Wolpert et al., 1995). The consequence of this chain of actions is that sensory events are analysed in terms of the appropriate motor response. Wall (1999c) suggests that there are

three evolutionary explanations for this system. It enables an individual to firstly remove the stimulus, secondly adopt a posture to limit further injury and optimise recovery and finally, seek safety and a cure.

However, if cortical remapping has occurred, resulting in a misrouting of sensory information, then errors will occur in the above system. In the case of an amputee, the predictor will continue to send motor commands and anticipate an expected sensory response, but sensory feedback from the amputated limb is no longer possible and, indeed, information concerning that limb may now come from other body structures. When this occurs, the system is alerted that there is a conflict between motor and sensory systems, and pain is experienced. Recently it has been shown that if this mismatch is corrected, using mirrors to provide the appropriate sensory response, then pain can be relieved in amputees and those with early CRPS (Ramachandran and Hirstein, 1998, McCabe et al., 2003b, see Chapter five).

This pain mechanism theory is still in its infancy, but its suggestion that pain can be experienced in the absence of pathology challenges the traditional view of a solely peripheral, nociceptive mechanism. It also enables us to reassess those perplexing conditions where pain exists in the absence of objective clinical findings, which may previously have been dismissed by a physician as 'psychosomatic'. These are predominantly chronic pain conditions where the doctors 'disbelief' may further compound the patients' distress.

### **1.8 Chronic pain and its psychosomatic implications**

It is important to recognise the difference between acute and chronic pain, as the latter is not simply a longer duration of the former. Melzack and Wall (1996g) state that chronic pain is the result of 'multiple, interacting causes', which commonly do not respond to treatments used successfully in acute pain. This inability to cure chronic pain may result in behaviour changes in the sufferer and they may describe a sense of helplessness or hopelessness. Keefe et al., (1980) describe the behavioural changes that may occur in the first two years of chronic pain, and how the initial hope for a cure gradually progresses to disillusionment and possible depression. This disillusionment sometimes results in 'doctor shopping', where the patient moves from one doctor to another

in the hope that a cure can be found. Fear, anxiety, depression and a sense of failure may ensue (Wall, 1999c). These changes may lead to the patient constantly scanning their symptoms, focussing more attention on the pain, which only confirms that their condition remains unchanged, or even perceived to be deteriorating. Catastrophising can be the natural consequence of this over attentiveness, so that minor changes become a noteworthy event, though for some, this may also act as a coping strategy (Keefe, et al., 1989).

Living with pain for a prolonged period can have a marked affect upon an individual and their quality of life: affecting relationships, employment, social activities and mood. These in turn can be influenced by gender, cultural beliefs, age and genetic factors. The confines of this thesis do not allow for a more comprehensive review of these areas, but this should not detract from their importance. Both physical and psychological factors interact and contribute to chronic pain. The relationship and balance between the two should always be considered when assessing and treating a patient in pain.

## **1.9 Rheumatology pain**

We have seen that the experience of pain derives from both peripheral and central mechanisms (at the spinal and cortical level), which may be greatly influenced by an individual's current and previous life experiences. Each mechanism, or external influence may require a subtly different therapeutic approach to relieve that pain and, ideally, the clinician would be able to identify the primary mechanism involved and target his or her therapies appropriately. The three brief case histories below will describe the signs and symptoms that a patient with RA, OA or FMS may present with, and illustrate how in practice, trying to identify one single cause is a futile exercise.

It must be stressed that our knowledge of pain mechanisms is far from complete and that much still relies on hypothetical conjecture.

### **1.9.1 Case history 1: Rheumatoid arthritis**

Patient A, a 42 year old woman, was diagnosed with sero-positive rheumatoid arthritis three years ago. She works as a teacher at the local primary school and lives with her husband and two teenage children in a two-

storey house. Until two months ago her disease was well controlled on 10mg of Methotrexate once a week. In addition she takes a non-steroidal anti-inflammatory drug once a day, and the occasional Paracetamol to ease pain and stiffness. She requests an early referral to her local Rheumatology department as she is now experiencing a 'flare' of her disease that coincided with the start of the Autumn school term. Her workload has increased due to staff sickness, and she is concerned about the impact this is having on her children at home.

She describes prolonged early morning stiffness, pain and swelling over her metacarpal phalangeal joints, wrists, knees and metatarsal joints. Her pain is predominantly burning in quality and she is tender to touch. She also reports generalised tenderness in her upper arms and legs. She finds it difficult climbing the stairs at home, and is kept awake by pain at night.

### **Possible pain pathways**

#### **Peripheral mechanisms**

The inflammatory process, as demonstrated by redness, swelling and local tenderness over Patient A's joints, will have generated peripheral sensitisation (primary hyperalgesia). Her report of burning pain suggests that this has involved her C-fibres or changes in the dorsal horn have resulted in central sensitisation. Her pain on walking up stairs may be due to changes in the intra-articular pressure within her knee joints, as an effusion may influence the mechanosensitivity of joint afferents, so that on movement, articular pressure is increased in a diseased joint (Schaible and Grubb, 1993).

#### **Central mechanisms**

The report of generalised tenderness indicates a lowering of the A $\beta$ -fibres threshold, which is characteristic of central sensitisation (secondary hyperalgesia), and may have been induced by the duration of her symptoms. Changes in proprioception due to joint damage and/or swelling of the joints may create a mismatch in motor and sensory systems, and this mechanism has been proposed as one explanation for the perception of stiffness in rheumatoid arthritis (Haigh et al, 2003, Appendix 2). Stiffness, as a distinct symptom separate from pain, has historically proved difficult to define. Three possible



definitions were tested and discussed during the generation of the current American Rheumatism Association diagnostic criteria for rheumatoid arthritis (Arnett et al, 1988), and all had relatively low specificity (Edworthy, 1999). However, a more recent patient-derived definition proposes that stiffness is a bilateral slowness or difficulty in moving the joints first thing in the morning or after prolonged sitting, which eases with movement (Lineker et al, 1999). Patient A's specific report of stiffness on rising would appear to meet this definition. Other factors that may be influencing Patient A's experience of pain and her ability to cope with it include her lack of sleep, anxiety regarding her workload and family life.

### **1.9.2 Case history 2: Osteoarthritis**

Patient B is a 75 year old gentleman with a five year history of pain in his left knee, and has radiographic changes suggestive of osteoarthritis. He lives alone and is finding it increasingly difficult to walk to the shops and manage around the home. He was a keen golfer but due to his reduced mobility has found that this is no longer possible. He describes intermittent sharp, stabbing pains in his left knee, occasional swelling associated with burning pain, and is concerned that his right knee is also starting to become painful.

#### **Possible pain pathways**

##### **Peripheral mechanisms**

Under normal circumstances nociceptors in the immediate vicinity of the intra-articular cavity do not induce pain when stimulated by mechanical pressure (Kellgren and Samuel, 1950). This explains why some patients with OA report little pain, despite severe radiographic changes (Kidd, 2003). However, these nociceptors can become sensitised in the presence of inflammation, leading to peripheral sensitisation as previously described. The sharp pain that Patient B reports may be attributable to the lowering of Aδ-fibre threshold so that previously benign mechanical stimuli become painful. In addition, bone is richly innervated with sensory fibres, and if oedema is present these too may be a source of his pain (Kidd 2003).

## **Central mechanisms**

The persistent peripheral sensitisation may result in central sensitisation, so that Patient B feels pain and tenderness extending beyond the area of his knee. Proprioceptive changes are inevitable due to the structural changes within the joint and the compensatory mode of walking Patient B will have developed. Sharma et al (1997) and Pai et al (1997) have both shown that patients with unilateral knee OA have worse proprioception in their affected and unaffected joints than elderly controls. This continuous sensory imbalance in the contralateral knee, increases the risk of injury and ultimately of generating OA (Hurley 1997) and this may explain Patient B's increasing concern regarding his right knee. His increasing social isolation and distress at his reduced independence will both influence his pain experience.

### **1.9.3 Case history 3: Fibromyalgia (FMS)**

Patient C, a 36 year old woman has recently been diagnosed with FMS. She is divorced and lives alone, but does have her elderly parents living nearby. She resigned from a clerical job on the grounds of ill health as she felt "too exhausted" to work, and State benefits are now her only source of income. She reports widespread pain and sensitivity, though is specifically tender over the characteristic FMS trigger points. She also reports that her hands and feet frequently feel swollen though when she looks at them they do not appear so. Her sleep is poor despite low dose Amitriptyline, and she complains of "an intense weariness", which is present all day. Her activity levels have reduced sharply and she relies on her parents to do all her shopping.

## **Possible pain pathways**

### **Peripheral mechanisms**

Despite Patient C's perception of swelling there is no inflammatory component to her disease, and this is more likely to be a central mechanism manifestation. Pain on deep palpation over the trigger points is also likely to be attributable to central sensitisation rather than peripheral, as is the presence of her generalised sensitivity (Staud et al 2001).

## **Central mechanisms**

Patient C's symptoms are highly suggestive of centrally generated pain though, with the cause of FMS still unknown, this can only be conjecture. Recent research increasingly suggests that neuroendocrine abnormalities may play a part in the generation of FMS pain. Her poor sleep and low exercise levels will reduce her natural production of endorphins, and changes in the activity of serotonin and noradrenalin may further compound this (Neek and Crowford, 2000). Her altered body perception may result in her actual sensory input no longer matching the efference copy, so that pain and other sensory disturbances are generated. These sensations may be exacerbated by her general anxiety concerning her financial pressures, reduced social contact, limited mobility, and the health of her ageing parents who are her only support system.

### **1.10 Conclusion**

The above case histories demonstrate the complexity of pain, and highlight the need for a comprehensive patient assessment that may necessitate multi-dimensional therapy. Patrick Wall stated that: "It is inherently ridiculous to consider pain as an isolated entity although many do exactly that. Our understanding brains steadily combine all available information from the outside world and from within our bodies... our personal ...and our genetic histories" (Wall, 1999c). Pain in the rheumatic diseases is no exception.

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## **CHAPTER TWO**

### **Review of Complex Regional Pain Syndrome**

#### **2.1 Introduction**

Chapter one has demonstrated the complexity of the mechanisms involved in the generation of pain and how these may manifest themselves in multiple symptoms. Complex Regional Pain Syndrome (CRPS) is a condition that epitomises these factors, with evidence of peripheral and central mechanism involvement displayed in a range of distressing symptoms, which may result in permanent disability for the sufferer. The pathophysiology of this condition has perplexed and fascinated pain researchers for decades, but its aetiology remains unknown and although approximately half of acute cases resolve spontaneously, the remainder will progress to the chronic form. The range of changes that occur in this condition (sensory and motor at both peripheral and central levels) without a major or ongoing nociceptive insult are inexplicable using our current pain theories. Understanding how CRPS is generated and perpetuated should greatly enhance our knowledge of pain mechanisms in general; this is where the focus of this thesis will now turn.

This chapter reviews our current understanding of CRPS, specifically focusing on the development of the diagnostic criteria, the presenting signs and symptoms, and how these relate to the recent theories on its pathogenesis and range of treatment modalities.

#### **2.2 Complex Regional Pain Syndrome**

##### **2.2.1 Taxonomy**

CRPS is the term now given to a group of painful conditions which were previously known as Reflex Sympathetic Dystrophy (RSD), causalgia, Sudeck's atrophy, algodystrophy, and many others whose names derived from the individual clinical signs and symptoms of these disorders, or the supposed pathogenesis (table 2.1). The unifying clinical features of these conditions include: pain with associated allodynia and hyperalgesia, oedema, autonomic and trophic changes, and loss of function (Scadding, 1999). Internationally, these names multiply still further, with the French having more than 30 names



**Table 2.1**

**Conditions included within the term complex regional pain syndrome**

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Acute bone atrophy	Post-traumatic painful osteoporosis
Algodystrophy	Post-traumatic vasomotor syndrome
Algoneurodystrophy	Reflex sympathetic dystrophy
Causalgia	Sudeck's atrophy
Migratory osteolysis	Shoulder-hand syndrome
Post-traumatic sympathetic dystrophy	Transient osteoporosis

for this syndrome, the Germans 50 and the Dutch 15 (Geertzen, 1998).

Causalgia is the oldest of these terms and was first used by Weir Mitchell to describe the changes he saw in the limbs of soldiers who had sustained severe nerve injuries from gun shot wounds in the American Civil war (Mitchell et. al., 1864). He described their limbs as glossy in appearance with colour changes, intensely painful with a burning quality and excessively sensitive to non-noxious stimuli (hyperaesthesia). He termed this condition causalgia from the Greek 'causos' for heat and 'algos' for pain.

During the 20<sup>th</sup> century the French surgeon, René Leriche, proposed that the sympathetic nervous system was involved in causalgia and other neuralgias which occurred following trauma (Schott, 1995). This was based on his observation that following injury to a peripheral nerve in an upper limb, a patient of his proceeded to develop diffuse pain, which spread beyond the territory of the single damaged nerve, and experienced changes in colour and sweating in the affected arm. These symptoms were greatly relieved following resection of the outermost wall of the brachial artery (sympathectomy), and therefore, Leriche concluded, that injury to the nerve plexus surrounding the blood vessel must determine the pain and other associated features (Leriche, 1939). However, he was aware that not every individual developed such symptoms following trauma, and he could only conclude that this was related to the temperament of the individual (Leriche, 1939). This variability in response between individuals has vexed researchers of CRPS ever since, but we will see in Chapter five, that this may now be explained by a greater understanding of pain mechanisms in general.

Leriche's finding resulted in many casualties of the first and second World Wars undergoing sympathectomies to provide analgesic relief (Schott, 1995). The potential benefit was assessed pre-operatively in some subjects, via administration of local anaesthetic blocks, which temporarily interfered with sympathetic outflow. If these were successful then surgery was indicated. No systematic randomised controlled trials were conducted at the time to assess the efficacy of these treatments, but these modes of therapy are still used and their efficacy, and the evidence supporting their use, will be discussed later under 'therapeutic options'.

In the mid-1900s Mitchell and Leriche were becoming increasingly aware that the clinical findings they saw in those with causalgia were also apparent in patients who had experienced trauma to a limb, but with no evidence of neural or vascular damage (Schott, 1995). This condition was initially termed as 'minor causalgia', but eventually went on to be called Reflex Sympathetic Dystrophy (RSD), as it was considered that the condition spread from the site of trauma, up to the spinal cord and then out via the sympathetic nerves (Nathan, 1980). The problem with this term was that not all patients responded to sympathectomies, and therefore the implied involvement of the sympathetic nervous system in the name RSD was problematic. Consequently clinicians started to use the terms sympathetically maintained pain (SMP) and sympathetically independent pain (SIP), to describe the variations in pathogenesis. To add to the confusion Sudeck described a very similar condition, focusing more on the features of osteoporosis that may be seen in this condition, which is now termed Sudeck atrophy (Sudeck, 1902).

These many terms continued to run in parallel, which led to confusion for the patient, as there was no consistency between doctors on the terminology of their condition, a lack of standardised entry criteria across research studies and consequently an inability to compare and contrast research findings to assess efficacy of treatments. In 1995 the International Association for the Study of Pain called a Special Consensus Workshop to address these issues, and consequently recommended a revised taxonomy, which would encompass all these diagnoses, so that clarity could be brought to the research and clinical settings (Stanton-Hicks et al., 1995). Their proposed new classification was based upon a descriptive rather than pathophysiological method, due to the lack of scientific understanding of the condition at the time. They selected the term complex regional pain syndrome, as 'complex' denotes the variety of clinical phenomena, 'regional' the distribution of the symptoms in these conditions, and 'pain', as this is a cardinal symptom of them all. Their definition states that CRPS is:

"A term describing a variety of painful conditions following injury which appears regionally having a distal predominance of abnormal findings, exceeding in both magnitude and duration the expected clinical course of the

inciting event often resulting in significant impairment of motor function, and showing variable progression over time.” (Stanton-Hicks et al., 1995)

This definition was then divided into Types I and II to differentiate between those whose symptoms follow known major nerve damage, (Type II, previously known as causalgia), and those where trauma has occurred, but no major nerve damage ensued (Type I, previously known as RSD) (see table 2.2 for exact criteria). The prerequisite on both conditions is that a diagnosis of CRPS is a diagnosis of exclusion and therefore all other possible causes of symptoms must be ruled out.

These criteria have been shown to be sufficiently sensitive so that they rarely miss an actual case of CRPS Type 1 (Perez et al., 2002) however, both internal and external validation suggest that CRPS is over diagnosed (van de Beek et al., 2002; van de Vusse et al., 2003). This has been attributed to the fact that a diagnosis of CRPS can be given based on subjective and even historical report of signs and symptoms (Harden, 2001). It has been recommended therefore, that the diagnostic criteria be amended to include motor/trophic characteristics (e.g. hair and nail growth changes, tremor and impaired limb function), and that a subject should demonstrate at least one symptom in this category, plus one in each of the other three diagnostic categories which are: vasomotor (temperature and/or skin asymmetry), sensory (hyperaesthesia), and sudomotor/oedema (sweating/ oedema in the affected limb only) (Bruehl et al., 1999; Galer et al., 1998). In addition, physician observed signs should also be evident in two or more of the categories. With these proposed changes the specificity of the criteria is greatly enhanced whilst losing little of its sensitivity; this is particularly important for research (Harden, 2001).

## **2.2.2 Clinical signs and symptoms**

CRPS Types I and II differ little in clinical signs, and therefore where the term CRPS is used in this section it should be assumed that this relates to both types unless otherwise stated.

**Table 2.2**

**Diagnostic criteria for complex regional pain syndrome.**

(Stanton-Hicks et.al., 1995)

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**CRPS type 1 (RSD)**

1. Type 1 is a syndrome that develops after an initiating noxious event.
2. Spontaneous pain or allodynia / hyperalgesia occurs, is not limited to the territory of a single peripheral nerve, and is disproportionate to the inciting event.
3. There is or has been evidence of oedema, skin blood flow abnormality, or abnormal sudomotor activity in the region of the pain since the inciting event.
4. This diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction.

---

**CRPS type 2 (causalgia)**

1. Type II is a syndrome that develops after a nerve injury. Spontaneous pain or allodynia / hyperalgesia occurs and is not necessarily limited to the territory of the injured nerve.
  2. There is or has been evidence of oedema, skin blood flow abnormality, or abnormal sudomotor activity in the region of the pain since the inciting event.
  3. This diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction.
-

Clinically, CRPS patients are a very heterogeneous population; although commonalities do exist there is great individual variance between the particular characteristics of symptoms and the extent to which they are experienced.

Typically CRPS affects the limbs with a distal to proximal regional spread that far exceeds the originating trauma. Spontaneous onset has also been described in a minority of patients (Veldman et al., 1993). Initially symptoms only affect one limb, but these may spread to the contra-lateral limb or other regions of the body (Baron et al., 2002). Three patterns of spread have been proposed: contiguous spread (gradual enlargement of the original affected area); independent spread (new occurrence of symptoms in an area which is distant and not connected to the initial site e.g. spread from hand to foot), and mirror-image (spread to the contra-lateral limb) (Maleki, 2000). There have been reports of patients experiencing CRPS type symptoms in the adjacent upper limb following mastectomy (Graham et al., 2002), and in the face, head and/or neck following trauma to the craniofacial region, though these are rare (Melis et al., 2002).

The common signs and symptoms can be divided into the four diagnostic categories stated above: sensory, vasomotor, motor/trophic and sudomotor/oedema.

#### **2.2.2.1 Sensory**

Pain is the overriding complaint of patients with this condition. It is disproportionate to the initiating event in terms of severity and duration (Scadding, 1999), and the distribution is not limited to individual nerve territories or the site of the originating trauma (Jänig and Baron, 2003). The pain may be exacerbated by movement, dependent posture and stress (Blumberg, 1994; Schwartzman, 1992; Jänig and Baron, 2003). In a recent study of 123 patients who met the criteria for CRPS, over 80% of the subjects described this pain as burning in quality (Harden et al., 1999). Patients also describe shooting, stinging, throbbing, pressing and aching sensations often associated with allodynia, mechanical and thermal hyperalgesia, hyperaesthesia, dysaesthesia and hyperpathia (Melis et al., 2002). This hypersensitivity may result in patients

being unable to tolerate clothing on a limb or the bedclothes at night. The intensity of pain can lead to a patient protecting their limb, and result in a severe loss of function. This will be discussed further under 'Motor/trophic' signs.

Occasionally patients will not present with pain. Veldman et al., (1993) reported that 7% of the 829 CRPS patients that they studied did not present with spontaneous pain, though they had experienced it at an earlier stage in their disease. This can lead to confusion and problems with classification, but historical report of symptoms would satisfy the current diagnostic criteria.

Quantitative sensory testing in patients with CRPS Type I has demonstrated a hemisensory impairment in the limb and upper quadrant of the body ipsilateral to the limb affected by CRPS (Rommel et al., 1999). This impairment was specific to temperature and pinprick, and occurred more frequently in those with left sided CRPS than right. Those patients who had the most extensive deficits were those with the longest disease duration, the highest levels of pain, the highest incidence of mechanical allodynia and a greater tendency to develop changes in the somatomotor system, than those with more limited sensory deficits (Rommel et al., 1999). The extent of the regional involvement of these deficits suggested to the authors that central mechanisms might play a part. In addition, evidence of these deficits may also be linked to the recent proposals that patients with CRPS demonstrate a type of 'neglect' (Galer et al., 1995; Galer and Jensen, 1999). Galer and Jensen (1999) suggest that those with CRPS Type 1 demonstrate both motor and cognitive neglect. These theories will be further discussed under 'Pathophysiology'.

#### **2.2.2.2 Vasomotor**

Reports of asymmetrical changes in colour and temperature are common in this condition. In Harden et al., (1999) 86.9% of patients described colour changes and 78.7% fluctuations in temperature. The limb is typically described as intermittently altering from blue and cold to red and burning, with associated mottling of the limb. Patients may also become very intolerant of changes in climate and water temperatures when bathing. It is sometimes difficult to establish whether a cold blue limb is the result of lack of use due to pain, or a

true reflection of the effect of the disease, and the clinician may be left to rely on the patient's subjective reporting to clarify this.

Three stages in the disease have been proposed whereby in the initial stage, (the denervation phase), the limb is warm, dry and highly perfused, progressing through to a second colder, sweaty, stage (hypersensitivity phase). In the final atrophic stage, the pain has become diffuse and muscle atrophy with distal osteoporosis has occurred, (Blumberg & Jänig, 1994; Scotence, 1995). However, as stated above, there is a wide variability in patients' symptoms, and in reality they do not always fit neatly into these categories (Scadding, 1999); some may never experience the warm phase and instead progress directly to the colder limb (Veldman et al., 1993).

#### **2.2.2.3 Motor/trophic**

Patients may report a weakness in the limb, stiffness of the joints, and develop fixed flexion deformities (Bonica, 1990; Wasner et al., 1998); these may result in a significant loss of function. There may also be a reduction in bone mineral density in the affected limb as described by Sudeck (1902). These changes could be attributed to the lack of use of the limb, as we will see under 'Pathophysiology'. Occasionally patients will report tremors, spontaneous jerks or dystonia with approximately 20% of the population studied by Harden et al. (1999), describing these symptoms.

Changes in the skin, hair and nails may also be present with the skin becoming either excessively shiny and thickened, or flaky and dry (Scadding 1999). Hair and nails may grow rapidly with ridging of the nails and thickening of the hair follicles, or conversely hair may become very thin, or completely absent, on the affected limb (Melis et al., 2002; Harden, 2001).

#### **2.2.2.4 Sudomotor/oedema**

Asymmetrical sweating of a limb with the affected limb exhibiting hyper- or hypohidrosis, is seen in both the acute and chronic stages of CRPS. Evidence of excessive sweating in chronic cases is particularly intriguing as the CRPS limb may, by this stage, be cool to touch with decreased skin perfusion. This suggests that the level of autonomic dysfunction is primarily within the



Central Nervous System (CNS), and interestingly, a similar phenomenon is seen in patients following a stroke (Naver et al., 1995; Hanger et al., 1996).

Oedema may also be present in the painful area, particularly early on in the condition, but this is thought to resolve in approximately half of all patients over time (Blumberg and Jänig, 1994). Oedema may limit function and contribute to the stiffness seen in the motor/trophic signs, but in turn may develop or be exacerbated by the reduction in limb movement due to pain. In cases of severe inflammation the skin folds may be lost and accompanied by tight, shiny skin (Blumberg and Jänig, 1994).

### **2.2.3 Diagnostic tests**

There are no diagnostics tests for CRPS that have proven specificity, and therefore diagnosis is based on a patient's signs and symptoms meeting the above clinical criteria and excluding any other condition (Baron et al., 1999). These signs and symptoms can be assessed via simple observation of the limb to note colour, presence/absence of oedema, hair and nail growth, altered sweating; assessing response to touch (light touch or pin-prick), to detect allodynia and hyperalgesia; recording patients' levels of pain on a simple Likert scale (Likert, 1952), and taking a detailed history to differentiate between CRPS Type I and II (Harden, 2001).

Blood flow differences between the affected and unaffected limbs can be quantitatively assessed either using infrared thermography, Doppler flowmetry or spot-temperature measurement (Harden, 2001, Baron et al., 1999). Plain radiographs may be used to determine signs of osteopenia, or DEXA three-phase bone scans, where changes in bone metabolism may be indicated by an increase in uptake of the tracer (i.e. reduced blood flow resulting in slow clearance of radioactive tracer) around the distal joints of the affected limb (Kozin et al., 1981). However, more recently the usefulness of three-phase bone scans as a diagnostic tool for CRPS has been called into question. The difference in tracer uptake is usually apparent only in the first year of the disease, and it has proved to have a poor predictive value (Davidoff et al., 1989, Mailis et al., 1994). Indeed, an retrospective chart review of 134 patients attending a pain clinic with CRPS, conducted by Allen et al., (1999),

demonstrated that of the 51 patients who had a bone scan only 51% were consistent with a diagnosis of CRPS.

In the past, a positive response to a sympathetic blockade was considered diagnostic. This procedure involves the injection of a local anaesthetic at the sympathetic ganglia to temporarily inhibit sympathetic tone in the extremity supplied by those ganglia. However, it has now been recognised that not all patients with CRPS have sympathetically maintained pain, therefore this was omitted as a diagnostic criteria in the most recent definition (Stanton-Hicks et al., 1995, Stanton-Hicks, 2001).

#### **2.2.4 Incidence**

The true incidence of CRPS is difficult to establish, as it is relatively uncommon and often misdiagnosed. However, the first and only population based epidemiological study of CRPS was conducted in Olmstead County, Minnesota (USA) (Sandroni et al., 2003). This initially identified subjects using the 1994 IASP criteria, (Merskey and Bogduk, 1994). Then the stricter, modified criteria by Harden et al. (1999) were applied, and subjects were re-classified. The authors reported a prevalence of 20.57 cases per 100,000, and an annual incidence of 5.46 new cases per year. There was a female to male ratio of 4:1, and a median age of 46 years at onset. Interestingly, the upper limb was affected twice as often as the lower limb, which is the opposite to its incidence in children, where the lower limb is affected more frequently by a ratio of about 5:1 (Scadding, 1999). All the subjects identified had experienced some triggering event with fracture being the most common cause (46%). If this data were representative of the total American population, then this would correspond to 15,000 new cases per year, and a prevalence of 58,000 cases in the USA alone (Bennett et al., 2003). These figures have been disputed by Bennett and Harden (Bennett et al., 2003) as 'unexpectedly low', and they cite a variety of reasons to explain this, including confusion in diagnostic criteria, as data were included prior to the 1994 definition of chronic pain states (Merskey and Bogduk, 1994); doubt that the region studied was, 'a typical population relative to the USA'; and that the use of a retrospective methodology led to a high exclusion of potential cases (81%), as insufficient data were documented in case notes. The authors of the original study (Sandroni et al., 2003) robustly

argue against these claims (Bennett et al., 2003), but clearly further studies are required to confirm the exact incidence.

In large, clinical studies following patients after limb fractures, the incidence rate varies greatly, depending on whether a retrospective or prospective study design has been used (Stanos Jr. et al., 2001). Following distal radial fractures, an incidence rate of 1-2% (retrospective study), or 10-38% (prospective study) have been reported (Atkins et al., 1990, Bickerstaff and Kanis, 1994, Field and Atkins, 1997). This variation in incidence has been attributed to the possibility that retrospective studies may miss the milder, resolving form of this disease that a prospective approach would capture (Stanos Jr. et al., 2001). The prospective study conducted by Bickerstaff and Kanis (1994) appears to verify this theory as, at 7 weeks post-distal radial fracture, 28% of their subjects met all areas of the criteria for CRPS, but by one year this had reduced to 1-2%.

The more complicated the surgery the greater the risk to patients of developing CRPS. Recent research has also focused on the possibility that the practice of immobilising a limb after fracture may in itself induce all the symptoms of CRPS (Butler et al., 1996, Guo et al., 2004). This will be explored further under 'Pathophysiology'.

### **2.2.5 Psychological factors**

Inevitably, the lack of understanding regarding the pathophysiology of CRPS has led physicians and researchers alike to question whether psychological factors contribute to this chronic pain condition, particularly as a seemingly minor injury can result in such intense pain. Providing conclusive evidence that psychological factors may trigger and/or perpetuate CRPS is problematic; ideally a prospective methodology is required to compare the pre- and post pain states, but CRPS is rare and therefore very few such studies have been conducted. Bruehl and Yung Chung (2004) are dismissive of the only published prospective study in this area (Zachariae, 1964), as the suggested predictive personality factors (e.g. 'unstable', 'ambitious', and 'sthenic') are hard to define. From their own clinical data on patients undergoing

total knee replacement (Bruehl and Yung Chung 2004), they have found no evidence that anxiety or depression were predictive of CRPS.

We have seen in Chapter one that living with chronic pain can generate psychological distress, and therefore it is difficult to establish once the condition is present, whether signs of psychological dysfunction are unique to CRPS or similar to those seen in other chronic pain states. Using a set of standardised measures of mood and illness behaviour, Ciccone and colleagues (1997), compared and contrasted patients with RSD to those with pain from an organic (local neuropathic pain) and non-organic cause (chronic back pain). They found that those with RSD did not have significantly higher levels of psychological distress than either of the comparison groups, and that levels of depression were nearly identical between the back pain and RSD groups. Interestingly, data from patients with RSD, for symptom reporting, illness behaviour, and psychological distress, were far closer to those with local neuropathic pain than the reports of more diffuse pain from the chronic back pain group. This led the authors to conclude that an organic, rather than psychological cause, of RSD should be sought.

Another small, comparative study with CRPS Type 1 patients, and those with chronic low back pain, looked for evidence and incidence of major psychiatric conditions, including personality disorders (Monti et al., 1998). They found that both groups had a high incidence of psychiatric disorders. Particularly major depressive and personality disorders, but there were no significant differences between the two groups. They concluded therefore that these psychiatric disorders were developed as the result of living with chronic pain, rather than evident prior to, or contributing to the development of, CRPS. This was consistent with other studies conducted in this area (Haddox et al., 1988), but without prospective data it is impossible to confirm.

In conclusion, there is no definitive evidence to suggest that psychological factors play a role in the development or maintenance of CRPS. This may be less clear in children, where one study has suggested that injury and the development of chronic pain may be a means of escaping parental expectation or stressful competition (Sherry and Weisman, 1988). This theory

would be supported by the fact that childhood CRPS is found more commonly in those who participate in competitive sports, but conversely this may simply mean that they are at greater risk of injury (Scadding, 1999).

### **2.2.6 Pathophysiology**

The mechanisms by which CRPS types I and II develop are still unclear. Theories and research have focused on both peripheral and central sources. However, as has been stated above, a key difference between the two exists, with type II only occurring after major nerve damage, and its characteristics unlike type 1, have been shown to closely match other animal models of sympathetically maintained pain (Jänig and Häbler, 2000; Jänig and Baron, 2001). This evidence of nerve damage, ensures that type II patients can be said to truly have neuropathic pain arising from changes that occur both at peripheral and central levels via the mechanisms discussed in Chapter one. There it was seen that damage in the peripheries could have a cascade effect resulting in central excitability and possible re-routing of information. These central changes will be further exacerbated if the damaged peripheral nerves do not regenerate appropriately, resulting in the death of many dorsal root ganglia (Jänig, 2001). These peripheral and central changes may eventually become irreversible but at what point this occurs is unknown.

The model above appears to be a logical mechanism for CRPS type II, and it fits well with other chronic pain conditions that arise from nerve damage. However, type 1 occurs following no major nerve damage, or indeed spontaneously, and therefore the same model cannot be applied. A multitude of systems are involved (e.g. inflammatory, sensory, somatomotor and sympathetic), and a plethora of research exists on this subject. For this reason, only the research that is relevant to the current theories on mechanism will be reviewed. For the remainder of this section where the term CRPS is used this will refer to type 1.

In a previous 'National Institute of Health Workshop' on CRPS, where leading researchers in the field and patient advocates were present, the general hypothesis put forward was that CRPS is a disease of the central nervous system (Baron et al., 2002). The justification for this hypothesis was that

patients with CRPS exhibit changes in systems which process tactile, thermal and noxious information as well as in the somatomotor and sympathetic systems, indicating that changes in central representation (i.e. where all these systems converge), must occur. However, how these central changes link with the peripheral inflammatory changes could not be explained, and this has always been the crux of the problem.

The most recent review of both human and animal experimental literature in this field has concluded, based partly on the work in this thesis, that a mismatch in central sensorimotor representation may be the key to understanding the mechanisms behind CRPS (Jänig and Baron, 2004). A paper, analysed within and published concurrently with this editorial review, described an animal model of CRPS whereby the hind limbs of rats were immobilised in plaster casts for a period of four weeks but only half the group actually had a fracture of the tibia (Guo et al., 2004). When the plaster casts were removed both groups had evidence of raised temperature, mechanical allodynia, periarticular osteoporosis and oedema in the casted limbs. However, the allodynia and increased temperature resolved more quickly in the rats that had not sustained a fracture (allodynia = 6 weeks resolution {non-fracture}, versus 10 weeks {fracture}; temperature = 2 weeks resolution {non-fracture}, versus 20 weeks {fracture}). Guo et al., (2004) proceeded to investigate how these signs and symptoms linked to the inflammatory response, particularly the role of the chemical inflammatory mediator substance P. They found that when an antinociceptive agent, which blocks the receptors of substance P (LY303870), was administered systemically and intrathecally, both modes of delivery reduced mechanical allodynia in the fracture and non-fracture rats, though it only reached statistical significance in the fracture group. However, this clearly demonstrates that substance P is released at the peripheral and central level, and that immobilisation of a limb is sufficient to trigger this effect.

The findings from this study link well with human studies on disuse and CRPS (Maeves and Smith, 1996; Butler et al., 1999; Butler, 2001) and demonstrate that immobility alone can produce its characteristic signs and symptoms. Interestingly, in human studies following limb fracture, subjects have also reported symptoms of neglect whereby they felt they lost control of their

affected limb unless they looked at it, and became less consciously aware of its existence (Butler et al., 1996). Galer and Jensen 1999) have also reported this phenomena in those with CRPS (see 'Clinical signs and symptoms').

Although the study by Guo et al., (2004) appears to provide a clear link between the peripheral and central changes that occur in CRPS, it has been suggested that the symptoms produced by immobilising a limb are not precisely the same as those of CRPS (Jänig, 2004). Indeed, when comparisons are made between those with CRPS and those immediately following distal radius fracture, some similarities were seen (both had mechanical allodynia in the affected limb and increased temperature), but there were also distinctive differences, with evidence of failure of sympathetic control (e.g. hyperhidrosis) only being present in the CRPS group. This led the authors to conclude that CRPS is not simply the result of an exaggeration of post-traumatic inflammation, but different mechanisms are involved in the generation of pain and vasomotor disturbances.

One of these other mechanisms may lie within the sensorimotor system. We already know that patients with CRPS have an altered perception of their limb and body schema (Butler et al., 1996; Galer et al., 1995; Galer and Jensen 1999; Schwoebel et al., 2001), and there is evidence that body perception may additionally be distorted by cortical reorganisation (Juottonen et al., 2002; Maihöfner et al. 2003; McCabe et al., 2003a, see Chapter four). These changes in sensory perception, as discussed in Chapter one (see 'Cortical remapping'), can generate a mismatch within the motor control system, between the predicted (efference copy) and actual sensory input resulting in the generation of pain (Harris, 1999). A recent paper by Moseley (2004) describes how a motor imagery programme (MIP) combining imagined hand movements, a hand laterality recognition task (Schwoebel et al., 2001) and mirror visual feedback (McCabe et al., 2003b see Chapter four), was used to activate the cortical networks which serve the affected limb in a small population of patients with CRPS. This cross-over design study compared routine care to the MIP, and found significant reductions in pain and swelling when subjects underwent the MIP, to the extent that six subjects no longer met the criteria for CRPS by the end of a twelve week treatment programme.

This thesis will continue to explore the paradigm that a sensorimotor mismatch is central to the cause of CRPS, but currently there are no definitive answers and further research, on both human and animal models is required. This includes research into possible genetic susceptibility where findings are currently inconclusive (Mailis and Wade, 2001). This is in part due to the complex problem of differentiating between the contribution of genes versus environmental and psychosocial issues in CRPS, and also in establishing what role genes play in the intricate setting of pain processing, where different systems may be involved in the generation, perception and perpetuation of pain (Mailis and Wade, 2001).

### **2.2.7 Treatment**

Guidelines for the treatment of CRPS were compiled in a consensus report in 2001 (Stanton-Hicks et al., 2001). The authors stress that multidisciplinary, early intervention is essential, with an emphasis on an individualised, flexible approach. The primary aim is to return the patient to normal function based on a gradual progression from gentle movements through to more challenging load bearing activities (Harden, 2001). "Stress loading" has been advocated by one group of Occupational therapists, which comprises active traction and compression exercises that are conducted whilst the subject scrubs a plywood board with the affected limb, and in a separate exercise, carry increasingly heavy weights (Watson and Carlson, 1987).

In addition to mobilisation of the limb, via physiotherapy, it is recommended that techniques to desensitise the limb also be employed (Stanton-Hicks et al., 2001; Harden, 2001). These involve touching the limb with fabrics of different textures and submitting it to varying water temperatures. These should all help to normalise the sensory processing which we have seen may be crucially important under 'Pathophysiology'. Sadly, no controlled trials exist on the efficacy of physio- and occupational therapy (OT), but one study has shown that physiotherapy when compared to OT and a control group, proved clinically more useful and less costly than its comparators (Severens et al., 1999).



### **2.2.7.1 Pharmacological management**

The use of pharmacological agents, via topical, oral or intravenous delivery, is primarily to provide sufficient analgesia for physical rehabilitation to take place. Recent trends have been towards a more mechanism based approach rather than the traditional empirical one. The inflammatory symptoms may be treated with non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids and free-radical scavengers such as vitamin C (Ribbers et al., 2003; Zollinger et al., 1999); but data is limited on their efficacy in CRPS with NSAIDs showing no effect in CRPS type 1 (Rico et al., 1987), and trials of vitamin C requiring further, larger studies to confirm efficacy. Corticosteroids were found to be effective early on in the disease, and may be useful when the limb is hot and oedematous, but again, data is limited (Kingery, 1997; Christensen et al., 1982; Stanton-Hicks et al., 2001).

When pain is present independent of stimulus, the suggested approach is to use treatments which will target the underlying sensitisation of the primary somatosensory afferents (Ribbers et al., 2003). These include opiates, sympathetic blockade, and ion channel blockers such as tricyclic antidepressants. Opioids and tricyclic antidepressants have been shown to be effective in other neuropathic pain states, but there have been no controlled studies in CRPS (Stanton-Hicks et al., 2001). The recommendation is that opiates should be tried earlier on in the disease than is currently the case and an intravenous trial, via patient controlled analgesia, may be helpful in establishing the levels of efficacy, before a longer term course of oral treatment is planned (Stanton-Hicks et al., 2001).

Sympathectomy, although traditionally used for the treatment and/or diagnosis of CRPS, actually has very little scientific support (Ribbers et al., 2003). Two systematic reviews of its use, primarily focusing on intravenous regional sympathetic blockade using guanethidine, showed that it was ineffective as an analgesic technique when compared to no treatment, or placebo (Jaded et al., 1995; Kingery, 1997). These findings may be partly due to methodological problems in study design, which ranged from poorly defined diagnostic criteria, to inadequate washout periods, or that only one block per

patient was used, whereas in clinical practice multiple blocks are common (Jaded et al., 1995; Kingery, 1997). However, in the review by Kingery (1997) one study, which was the most methodologically sound, delivered one, two or four guanethidine blocks per patient, and showed no difference in efficacy when multiple blocks were used (Ramamurthy et al., 1995). In those patients where benefit is gained, it is usually only transient with patients reporting analgesic relief for a matter of hours or days, and some may actually experience an increase in pain (Scadding, 1999). Small studies with drugs other than guanethidine (ketanserin and bretylium) have shown some analgesic benefit, but more research is required to verify these findings (Kingery, 1997).

Sympathetic ganglion blocks (stellate ganglion block for upper limb and lumbar sympathetic block for lower limb CRPS) are also used for the treatment of pain. The only placebo controlled, randomised study reported that initial pain relief was equal to that of placebo, but it lasted nearly four days in the treatment group, compared to one in those receiving normal saline (Price et al., 1998). Sympathectomy, (surgical, chemical or radiofrequency), has been shown to be effective in the short term, but pain relief is not sustained in the longer term (Scadding, 1999). This may be related to the time at which the procedure is performed in relation to disease duration. Schwartzman et al. (1997), in a prospective study of 29 patients with CRPS following injury, reported a significant relationship between successful outcome and symptom duration. 100% of patients with symptoms  $\leq$  one year were deemed to have had a successful outcome (visual analogue score for pain  $\leq$  2), compared to 44.4% with symptoms  $\geq$  than two years. However, they do not define what is meant by 'long-term satisfactory outcome', so it is difficult to assess the extent to which these improvements were sustained. Importantly, this procedure may not be innocuous, with some subjects reporting a new pain days or weeks after the sympathectomy (Kramis, 1996). This pain is usually located in the proximal area of the affected limb, and may extend on to the trunk with associated sweating and allodynia (Raskin et al., 1974; Scadding, 1999). This condition occurs in approximately 30-50% of subjects, and may induce pain which is worse than the original complaint (Scadding, 1999).

Carbamazepine, a sodium channel blocker, and Gabapentin, a calcium channel blocker (see Chapter one, 'Peripheral and central sensitisation') have also been tried in CRPS, but again there are no specific randomised trials (Harden, 2001). A small study of nine patients with RSD, using Gabapentin (900mg to 2400mg per day), reported sustained pain control and some improvements in skin colour and temperature regulation (Mellick and Mellick, 1995), but further, larger studies are required.

When pain is evoked by stimulus, treatments should be targeted at reducing central sensitisation with drugs such as ketamine and amantadine (Ribbers et al., 2003). These are NMDA receptors, which we saw in Chapter one are involved in 'wind-up' and central sensitisation. However, these drugs are known to cause significant side effects, with patients describing such experiences as hallucinations and vivid dreams, and no controlled trials have yet been conducted in patients with CRPS (Ribbers et al., 2003).

The use of nasal calcitonin in the management of CRPS has been studied the most (Gobelet et al., 1986; Gobelet et al., 1992; Bickerstaff and Kanis, 1991); two of the studies showed no benefit compared to placebo (Gobelet et al., 1986; Bickerstaff and Kanis, 1991) and one, some (Gobelet et al., 1992). These differences in outcome have been attributed to the different modes of assessing pain, with the positive trial data using qualitative techniques and the negative ones, quantitative (Kingery, 1997). Clinically, the experience has mimicked the more negative findings (Harden, 2001). Subcutaneous injection of calcitonin has shown no differences in reduction of oedema compared to placebo, and if any analgesic effect is seen then this is apparent very early on, so repeated injections over a course of treatment cannot be justified (Stanton-Hicks et al., 1998). The use of intravenous bisphosphonates, such as pamidronate and alendronate, have been shown to reduce pain and oedema, and increase range of movement when compared to placebo (Adami et al., 1997). However, this study only involved small numbers (20) and had a short follow-up (six weeks). Studies using repeated infusions (60mg per day for 3 days) have also shown a reduction in pain and enhanced function but no placebo controlled data is yet available (Kubalek, 2001).

The topical use of capsaicin is less commonly used and supported only by case report (Ribbers and Stam, 2001). Although capsaicin initially produces a flare response, repeated use leads to a reduction of nociceptive sensitivity with a subsequent hypoalgesic effect. Further studies are required to confirm its usefulness in CRPS.

#### **2.2.7.2 Psychological interventions**

Due to the stress of living with chronic pain, it is thought that by six months disease duration, all patients will display varying degrees of anxiety, depression and disturbed sleep (Stanton-Hicks et al., 1998). It is recommended that treatment be targeted towards supporting the patient by providing a clear diagnosis, information and education about their disease, realistic goal setting and where possible, the patients' partner and/or other family members should be involved in this. This may be delivered on a one-to-one basis, or in a group setting (Stanton-Hicks et al., 1998). Some of the medications outlined above may be helpful with reducing depression; particularly the tricyclic antidepressants, and cognitive behavioural therapy, or psychotherapy, may also be beneficial. Many patients exhibit kinesophobia, fearing to move their limb, and therefore particular attention should be given to normalising limb movement (Harden, 2001). The importance of recognising these aspects of a patient's care cannot be over emphasised. Often engagement in physical rehabilitation, and progress to recovery is not possible when there are significant psychological barriers (Harden, 2001).

#### **2.2.7.3 Other interventions**

Spinal cord stimulation (SCS) has in recent years been used to try to relieve pain and improve function in CRPS. In an evidence-based review of the literature, the conclusion was that data is too limited to give a clear indication on the usefulness of this technique as an analgesic therapy (Grabow, 2003). The only randomised trial, involving patients with chronic disease duration, compared SCS plus physical therapy versus physical therapy alone. The authors concluded that SCS provided no long term benefit on detection and pain thresholds of pressure, warmth or cold, and had only minimal benefit on mechanical allodynia (Kemler et al., 2001). This invasive, potentially high risk procedure appears to have little to support its use at present.

Perhaps the most controversial treatment of all is that of amputation. This sometimes becomes inevitable if the limb becomes untreatably infected (Geertzen et al., 1997), but may be requested by the patient to improve function. In the only reported study of RSD patients receiving amputation for persistent infection, pain or improved function, the results were not promising (Dielissen, 1995). Of the 28 patients involved, a total of 34 amputations were performed. In 28 of these RSD recurred in the stump, resulting in only two patients being able to wear a prosthesis. Intriguingly the authors report that despite these outcomes, 24 of the patients were satisfied with their results.

The use of motor imagery and mirror visual feedback have briefly been discussed above and will be covered further in Chapter four. These novel approaches to such an intractable pain condition may provide a new avenue of therapeutic delivery, which is clearly needed when so few other effective options are available.

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## **CHAPTER THREE**

### **Methodology**

This Chapter will provide a description of the methodologies used which were common to all three research studies. These were participant recruitment and ethical approval. The areas which were investigated were: the exploration and characterisation of referred sensations in CRPS (Chapter four), a trial of mirror visual feedback in CRPS (Chapter five), and the simulation of sensory-motor incongruence in healthy volunteers (Chapter six). Where specific variations occurred (e.g. measurement of pain in Chapter four, and description of exercises performed in Chapter five), these are described later at the appropriate stage within the relevant Chapter.

#### **3.1 Participant selection and recruitment**

##### **3.1.1 Patients**

The research studies described in Chapters four and five both involved patients with CRPS type I. The reason for selecting type I rather than type II was that the purpose of my studies was to explore pain that occurs in the absence of nociceptive insult. Type I occurs in the absence of major nerve damage. All patients were recruited from the Royal National Hospital for Rheumatic Diseases, Bath, UK. This is a small specialist NHS Trust, which has a tertiary referral service for those with CRPS. This inevitably means that we see the full range of the disease, from acute to chronic. Sadly, due to the inadequate diagnosis of this condition, our referrals are predominantly those with chronic disease, who have received multiple previous treatments with little or no benefit. It is difficult to establish whether the specialist nature of our service incurs a referral bias to my study population, with the more severe form of the disease dominating, as little knowledge exists concerning the epidemiology of the UK CRPS population. Anecdotal reports from RSD UK (a large patient support group for those with CRPS), suggest that the majority of their members receive a diagnosis one to two years after symptoms present, and that these symptoms respond poorly to current treatments. The similarities in these external reports to our patients' demographics, suggest that the

subjects involved in my studies may be similar to those in the wider population with chronic disease, but may not be to those with the acute resolving CRPS. The rarity of the condition (see Chapter two) also means that we only see approximately 8-10 new cases per year. For this reason the two studies involving patients were run concurrently, and those who wished to participate, and met the entry criteria, were consecutively recruited in to both studies.

I invited patients to participate in the research when they first attended the hospital, either for outpatient or inpatient care. The rationale behind which type of care a patient receives (inpatient or out patient) is not simply dependent on the severity of their symptoms. As the RNHRD is a tertiary referral centre, many patients travel a considerable distance to receive care, and therefore an inpatient stay may be the most practical option for them. This fact should be remembered when reading the studies relating to these participants.

#### **Inclusion and exclusion criteria**

Adult ( $\geq 18$  yrs) participants who conformed to the IASP diagnostic criteria for CRPS Type 1 (Stanton-Hicks et.al., 1995) in a single limb were considered eligible. Single limb involvement only, was essential as visualisation of the unaffected limb was key for the use of mirror visual feedback (Chapter five). Those who had any evidence of a peripheral nerve lesion (CRPS type II), co-morbidity which may influence their pain (e.g. diabetic neuropathy), and/or an asymmetrical visible disfigurement on their unaffected limb, were excluded.

#### **Sample size**

There has been no previous research in these areas of study in a CRPS population. The only similar work has been conducted in those with amputee phantom limb pain (PLP), and these were limited case reports or involving only small study populations ( $\leq 16$ ; Ramachandran and Hirstein, 1998). It was therefore difficult to estimate sample sizes accurately, which would detect the incidence of referred sensations in CRPS, and significant changes in pain with mirror visual feedback. Interestingly, Ramachandran, the author of similar work in PLP, has specifically advocated the study of individual cases or small sample populations in depth and with careful observation, when conducting exploratory studies of this nature (Ramachandran, 2003). The reliability of any findings can



then subsequently be tested in a larger population. For the reasons stated above, the two studies described here were conducted as exploratory pilot studies, using a qualitative methodology. Bowling (1997) states that this methodology is essential 'for exploring new topics and gaining insightful and rich data on complex issues'. Expert statistical opinion from the Bath Research and Development Support Unit confirmed that this was the most appropriate methodology to use. Therefore a non-random sampling strategy was applied (purposive sampling), as the aim of these studies was to generate hypotheses rather than apply the findings of the studies to the wider population. These hypotheses can then be tested at a later date using quantitative methodologies to assess whether any initial findings are applicable in a wider population. A purposive sampling approach (Bowling, 1997) was considered the most appropriate sampling strategy as this involves the deliberate selection of a population with particular characteristics. Therefore all patients with CRPS who attended the hospital over a two year period were screened for inclusion. By employing this method it was recognised that the generalisation of the findings may be limited.

### **3.1.2 Healthy volunteers**

The third research study (Chapter six) involved only healthy volunteers. These were recruited from the hospital staff, visitors and family members of patients at the hospital. This was done via word of mouth, internal email, and poster advertising in the entrance to the hospital. As this was an exploratory study, no specific age or gender was targeted, but by using a range of recruitment techniques, it was anticipated that this would capture people of all ages.

### **Inclusion and exclusion criteria**

Healthy adults ( $\geq 18$  years) with no current or past illness that would influence their proprioception (e.g. neurological), and who had no asymmetrical visible disfigurement on their upper or lower limbs were invited to participate. This latter criterion was required so that when visualising the reflection of a single limb in the mirror, the participant could truly believe that this reflection was their hidden contralateral limb.

## **Sample size**

This was a novel research study with no previous pilot data from which to base a sample size calculation. The only other study involving healthy individuals, and the same visual manipulation technique, used sophisticated imaging to collect data, rather than descriptive analysis of subjects' reports (Fink et al., 1999). This study was therefore conducted as an exploratory pilot study, using a purposive sampling technique for the same reasons as described above (see Patients – Sample size). To ensure that the widest range of possible descriptors were collected, data collection continued until data saturation had occurred; that is until no additional new sensations were reported. However, it was recognised that by employing a non-random sampling method, the generalisability of the findings may be limited (Bowling, 1997).

## **3.2 Ethical considerations**

The primary focus of any ethical consideration must be to ensure that participants are able to decide for themselves whether they wish to enrol in research or not, and that respect is given for the individual's autonomy (Streiner and Norman, 1999). To achieve this, there must be informed consent, which is that the subject understands that it is research they are participating in, the purpose of that research, and their contribution to it. They must also not feel coerced into participating. This is of particular relevance when their treating clinician may be involved in the recruitment process. In this scenario the subject may feel obliged to participate due to concerns regarding their continued care if they refuse. Or that they accept out of a sense of gratitude for the care they have already received (Streiner and Norman, 1999). To ensure that these issues were addressed appropriately, and to meet the standards of Good Clinical Practice guidelines, full ethical approval was sought and granted from the Bath Local Research Ethics Committee prior to the commencement of any research. Further internal approval was also sought from the hospital's Research and Development committee. Documents that were developed to comply with informed consent, and included within the above applications were: participant consent forms and information sheets (Appendices 3-6), and a General Practitioner information sheet for the study, where a potential therapeutic intervention was used (mirror visual feedback) (Appendix 7). Clear

explanation of the nature of the research, and the subjects' involvement within it, were included in these.

I personally recruited all participants, and although I was partly involved in the delivery of care for those receiving treatment at the hospital, I was not the lead clinician. Following an invitation to participate in the research, all subjects were provided with written and verbal explanations of the relevant study, and time was given to answer questions. It was also stressed that subjects could withdraw at any time from the research, and that this would not influence their continued care. The healthy volunteers were informed that they were providing comparative data for a study exploring pain in rheumatology conditions. This was to ensure that they were 'blinded' as far as possible and within ethical limits, to the purpose of the research in order to limit any preconceived expectations. Clearly this could be construed as deception and against the principles of informed consent (Bulmer, 1982), but a clear explanation of the procedures and possible consequences were provided. This methodology was deemed essential to guarantee data quality.

The following chapters will now describe the three research studies in which the above subjects were involved, and the specific methodologies used.

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## **CHAPTER FOUR**

### **Referred sensations in patients with Complex Regional Pain Syndrome Type 1**

(Appendix 8; McCabe et al., 2003)

#### **4.1 Introduction**

Chapter two has shown that CRPS Type 1 is a complex condition with a multitude of signs and symptoms. These include for some patients, an altered perception of their affected limb and body schema (Galer et al., 1995; Butler et al., 1996; Galer and Jensen 1999; Schwoebel et al., 2001). These reports are very reminiscent of those given by amputees where post-operatively, an amputee may perceive a phantom limb that has all the same sensations and mobility of the real limb prior to amputation, and is so strikingly real to the individual that it feels an integral part of them. The phantom appears to 'inhabit the body' (Melzack, 1990) when the eyes are open, and moves appropriately with other limbs. It initially feels perfectly normal in size and shape, but may alter over time so that the phantom gradually becomes less apparent and may eventually fade away (Katz and Melzack, 1990).

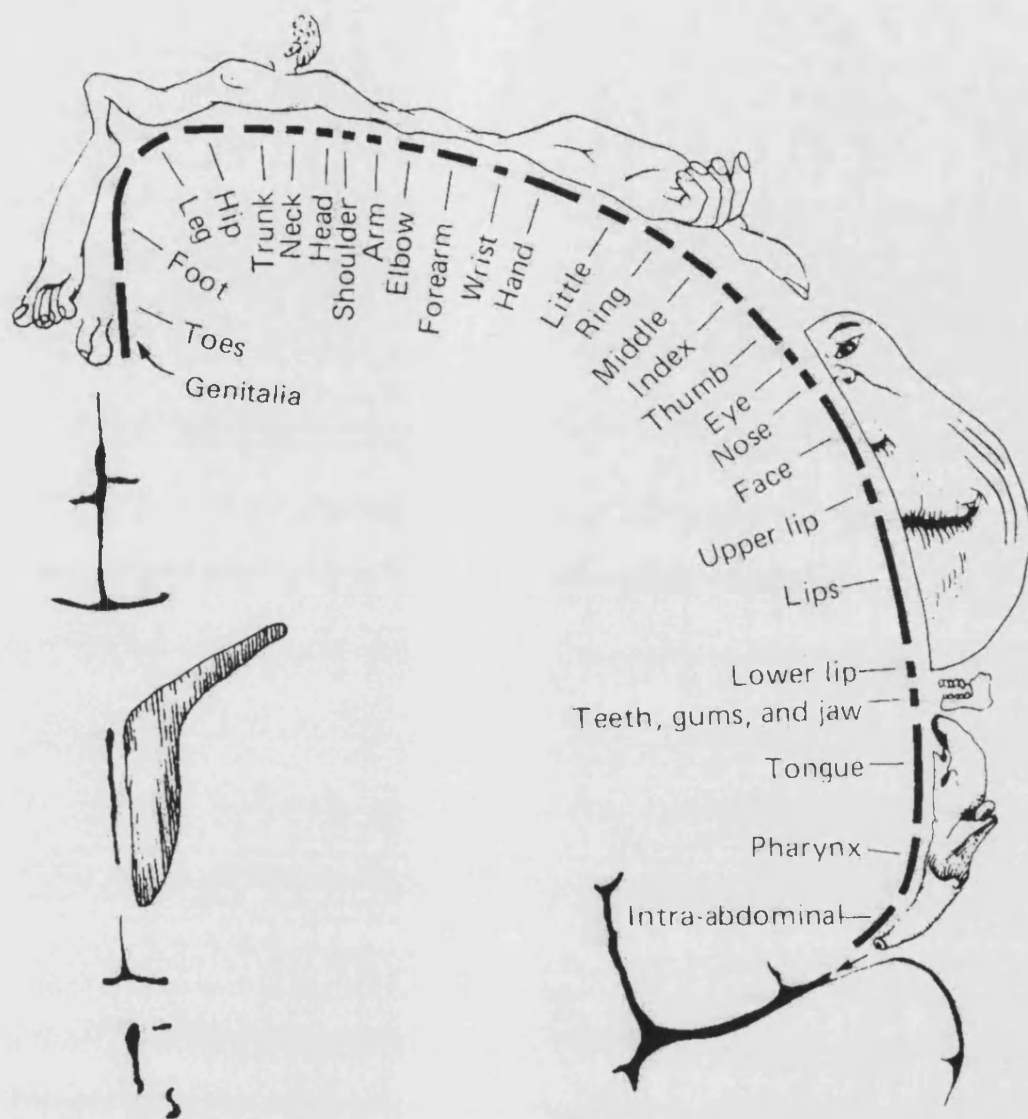
The type of pain that amputees report is also very similar to that of those with CRPS. Phantom limb pain (PLP) is a phenomenon that occurs in approximately 70% of patients after amputation (Halbert et al., 2002). For the amputee 'these pain memories are vivid, perceptually integrated experiences, which incorporate both emotional and sensory aspects of the pre-amputation pain' (Hill et al., 1995). Tingling is the most common complaint, but pins and needles, shooting, burning or crushing pain have all been reported (Melzack 1971). One characteristic recently described in PLP, which has not been previously described in CRPS, is that of referred sensations.

As was briefly alluded to in Chapter one, referred sensations (RS) are somatosensory feelings that are perceived to emanate from a body part other than, but in association with the body part being stimulated. In the case of

amputees, patients with upper limb amputations have reported sensations in their phantom hand when parts of the face, ipsilateral to the amputation, are lightly stroked (Ramachandran et al., 1992). These aberrant somatosensory, but reliable sensations were interpreted as resulting from central sensory reorganisation following disconnection or dysfunction of sensory pathways, (Ramachandran et al., 1992) as the hand lies between the face and trunk on the sensory homunculus (Penfield and Rasmussen, 1950) see Fig 4.1.

Ramachandran et al. (1992) proposed that this mislocalisation was a direct perceptual correlate of an invasion of sensory inputs from the face and trunk into the hand area. Cortical reorganisation of this nature was originally described in animal experiments (Merzenich et al., 1984; Pons et al., 1991), and Ramachandran used magnetoencephalography (MEG) to provide objective evidence of these changes in humans (Ramachandran 1993). Interestingly, those with a congenitally absent limb and no phantom sensations have not been shown to have the same cortical changes as those with traumatic amputation (Montoya et al., 1998). There is also evidence that the degree of phantom pain experienced has a direct linear relationship to the extent of reorganisational shift (Knecht et al., 1996).

Referred sensations have also been reported following somatosensory deafferentation (Clarke et al., 1996) local anaesthesia, (Gandevia and Phegan, 1999), stroke (Turton and Butler, 2001), and spinal cord injury (Moore et al., 2000). Collectively these studies have shown that the referred sites (the body part not physically touched) are non random, and like those of amputees, closely correspond to the body structure which is immediately adjacent to the stimulated site on the cortical topographical map first described by Penfield (Penfield and Rasmussen, 1950). Evidence of neural plasticity in other chronic pain conditions, such as focal hand dystonia (Lenz and Byl, 1999) and repetitive strain injury (Byl and Melnick, 1997), suggests that the disturbed peripheral sensations in CRPS (Type1) should also be associated with central sensory changes.



**Fig. 4.1.** The Penfield 'homunculus' demonstrating the proximity of the hand to the face. Penfield and Rasmussen, 1950.

The research study presented in this Chapter tested the hypothesis that central sensory reorganisation occurs in patients with CRPS, and that these changes would be evident in some patients as referred sensations. Furthermore, these referred sensations would be perceived to emanate from the body structures immediately adjacent to the stimulated site, and in keeping with their topographical location on the Penfield homunculus, as in phantom and allied pain states.

Only those patients with CRPS Type 1 were selected to specifically discover whether central reorganisation occurs even where there is no evidence of local peripheral nerve damage. This study therefore set out to explore and characterise referred sensations in patients with CRPS (Type 1). Five case studies are presented where referred sensations were found to exist.

## **4.2 Method**

### **4.2.1 Participants**

See Chapter three for inclusion/exclusion criteria and ethical considerations.

### **4.2.2 Clinical method**

Subjects were assessed for referred sensations on initial presentation and weekly until either symptom resolution occurred or, in those with chronic disease, discharged from inpatient care. Each assessment took the following format:

Subjects were positioned in a supine position with the head of the couch elevated so that they could view all their limbs. They were asked to close their eyes and describe to the researcher any sensations they were experiencing, first in their unaffected limbs and then their affected limb. This first stage was used to accustom the subjects to focusing upon themselves and to establish baseline descriptions for unaffected limbs. It was essential that the subjects' eyes were closed as visual feedback, of a researcher touching a limb, is known to diminish or suppress referred sensations and other changes in body schema (Hunter et al., 2002). As this was a novel exercise for the subjects to perform



care was also taken to stress that there were “no wrong or right answers”, and that they should simply relate what they felt. Where the upper limb was affected the subject was first questioned about their legs, followed by their unaffected upper limb and finally the affected limb. Conversely when the lower limb was involved the upper limbs were described first. This order was employed to ensure that the subject was familiar with the reporting process before the limb of interest was described.

All subjects then underwent a standardised neurological examination testing light touch, pinprick and vibration sense first with their eyes closed and then with their eyes open. Pinprick was tested using a ‘Neurotip’; light touch was assessed with a cotton bud gently brushed against the skin; and vibration was with a standardised tuning fork. This technique was selected as it complied with similar investigations in PLP (Ramachandran and Hirstein, 1998). All limbs, lower spine and face were examined, sham trials, combined with a random order, were employed to reduce the possibility of patient suggestibility. Each time the subject was touched they were asked to describe the location of the stimulated site, the sensation emanating from it and whether they experienced any sensations (similar or different) anywhere else. Sham trials simply involved not touching the subject but still asking them what sensation they felt whilst they had their eyes closed. When their eyes were open this technique could not be employed.

### **4.3 Results**

Over the two year recruitment period sixteen subjects (13 female, 3 male) who met the entry criteria were recruited. Only five showed evidence of referred sensations and it is the findings of these five (four females and one male) that will be presented (table 4.1). Routine clinic data showed that there was no difference in age, disease duration, levels of pain, or severity of disease (table 4.2) between those who presented with RS and those who did not.

**Table 4.1 Details of the five patients who showed evidence of referred sensations**

Patient	Pain site	Disease duration	Area touched (1) Referral site (2, 3)	Direction of referral	Type of sensation	Loss of referred sensation	Resolution of CRPS (wks)
Case 1 28yrs F (Fig 4.2a)	Left hand	3 wks	L 3 <sup>rd</sup> fingertip (1) L lower jaw (2)	1-2	Light touch & pinprick	3 wks	6
Case 2 34 yrs F (Fig 4.2b)	Left ankle	8 wks	L forefoot (1) L patella (2)	1-2 & 2-1	Light touch & pinprick	3 wks	4
Case 3 24yrs M (Fig 4.2c)	Left knee	3 yrs	L patella (1) L forefoot (2)	1-2 & 2-1	Light touch	No change	Chronic
Case 4 41yrs F (Fig 4.2d)	Right foot	6 yrs	R forefoot (1) R patella (2)	2-1	Light touch	4 wks	Chronic
Case 5 57yrs F (Fig 4.2e)  (Fig 4.2f)	Left hand	4 yrs	L shoulder (1) L ear (2) L hand (3)  L cheek (1) L hand (2)	1-2 1-3  1-2	Pulling, light touch & hand movement  Light touch	No change	Chronic

**Table 4.2 Details of all 16 patients**

<b>Case</b>	<b>Age</b>	<b>Gender</b>	<b>Disease duration</b>	<b>Affected limb</b>	<b>Pain level on movement*at presentation</b>
<b>1 **</b>	28yrs	F	3 wks	Left hand	8
<b>2 **</b>	34 yrs	F	8 wks	Left ankle	8
<b>3 **</b>	24yrs	M	3 yrs	Left knee	8
<b>4 **</b>	41yrs	F	6 yrs	Right foot	9
<b>5 **</b>	57yrs	F	4 yrs	Left hand	5
<b>Mean **</b>	<b>36.8yrs</b>	<b>4F:1M</b>	<b>2.6yrs</b>		<b>7.6</b>
<b>6</b>	38yrs	F	6 wks	Left ankle	9
<b>7</b>	35yrs	F	5 mths	Right arm	5
<b>8</b>	40yrs	F	1 yr	Right arm	6
<b>9</b>	38yrs	F	3yrs	Left leg	5
<b>10</b>	27yrs	M	2yrs	Left leg	8
<b>11</b>	51yrs	F	2yrs	Right arm	7.5
<b>12</b>	68yrs	F	1yr	Left arm	5
<b>13</b>	54yrs	M	4yrs	Left foot	9
<b>14</b>	38yrs	F	7yrs	Left foot	10
<b>15</b>	22yrs	F	4yrs	Left foot	9
<b>16</b>	59yrs	F	10yrs	Left foot	9.5
<b>Mean</b>	<b>42.7yrs</b>	<b>9F:2M</b>	<b>3.1yrs</b>		<b>8</b>

\*Visual analogue 10cm scale \*\* Referred sensations reported

The five subjects had disease durations of 3 weeks to 6 years (median 3 years) and were aged from 24 to 57 years (mean 36.8 yrs). Each had a single limb affected (2 upper limb, 3 lower limb). In four cases (Cases 1, 3, 4 & 5) the condition was spontaneous in onset and only in Case 2 did it occur following injury. All reported pain that extended beyond the originating site with associated allodynia, hyperalgesia and vasomotor changes. None of the subjects had ever reported any previous perception of referred sensations to their physician.

#### **4.3.1 Case 1**

A 28 year old woman was admitted for inpatient rehabilitation with a three-week history of progressive pain in her left hand for which there was no obvious triggering event. Her initial symptoms prior to the onset of pain, were that of mottling of the fingertips. An intense burning pain involving all four fingers, but excluding the thumb, rapidly followed. Cold and light touch aggravated the pain and feeling of swelling. The patient held her limb in a flexed and pronated position close to her chest. Her hand was cold to touch and quantitative thermal imaging (a routine clinical procedure) identified a 2.0°C temperature difference between the right and left forearms with the left cooler. Difference is considered significant when  $\geq 0.4^{\circ}\text{C}$  (Uematsu et al., 1988).

With her eyes closed she described her hand as excessively large 'like a blow up hand'. This phantom sensation of swelling extended to the thumb, despite no perceived involvement of this digit in her pain description. The patient was aware that this sensation was disproportionate to the degree of swelling that she observed. When the tip of the third finger of the affected hand was touched with a cotton bud, still with eyes closed, she experienced a stroking sensation over the lower left jaw (Fig. 4.2a). This sensation was modality specific with the subject reporting a pinprick sensation on her lower left jaw when the same finger was touched with a needle. The referred sensation only occurred at the time that the third finger was touched and there was no residual effect once the researcher stopped. Vibration was not referred. When the subject's left lower jaw was touched there were no reciprocal referred sensations experienced in the left hand.

The above examination was repeated with the subject looking at their hand as their affected limb was touched. Permitting direct visual feedback prevented the experience of referred sensations. Over the next two weeks the referred sensations could be evoked at each assessment. However, by week three the subject no longer perceived her hand as swollen and referred sensations were lost. By six weeks all vasomotor changes were reversed and no pain was felt.

#### **4.3.2 Case 2**

A 34 year old woman presented to the outpatient department eight weeks following an industrial accident, Having sustained a minor injury to her left foot but no neural trauma. The initial pain of the injury settled, but returned two days later. On admission she described a stabbing pain from the toes to mid calf. The foot was swollen, mottled in colour, hyperalgesic, allodynic and hyperhidrotic. The foot and calf were cold to the touch. Quantitative thermal imaging showed a 2.5°C difference between the right and left foot.

With her eyes closed the subject noted that her left foot appeared enlarged, greater in size than when she looked at it. During examination for referred sensations she reported that when her left knee was touched with a cotton bud she felt a similar sensation on the plantar aspect of her left foot, around the base of her metatarsalphalangeal joints (MTPs) (Fig. 4.2b). When this area on her left foot was touched a similar sensation was experienced in her left knee. She had not sustained any injury to, or experienced any pain in this knee, at the time of her accident. The reality of these referred sensations was such that the patient was able to differentiate between light touch and pinprick sensory modalities at both referred sites. There were no referred sensations reported for the non-painful lower limb. Again, when the subject watched the examiner touch her affected limb no referred sensations were reported.

This bi-directional referral of sensations could be evoked at the next two assessments but by week three following intensive physio- and hydrotherapy,

the subject's pain and swelling had greatly improved and referred sensations were lost.

#### **4.3.3 Case 3**

A 23 year old man was referred and admitted for rehabilitation. Three years previously he had woken with a spontaneously swollen left knee. No evidence of arthropathy was found despite full investigation, including arthroscopy, synovial biopsy and MRI. He was aware of an extreme burning pain and the knee felt as if a 'red hot poker' was touching it. This pain persisted for eight months and was unaffected by analgesics or steroid therapy. He had a nerve block, which improved his symptoms for approximately 15 months. He then noticed colour changes in his left ankle and increasing tenderness. Two weeks later his knee became painful again. He underwent a wide number of different therapies (physiotherapy, TENS, acupuncture, nerve blocks) all of which had little or no effect upon his symptoms.

On admission he complained of intense burning pain in his left knee and ankle, was reluctant to move his leg and walked on crutches. Both his left ankle and left knee joints were moderately swollen and mottled in colour. He complained of hyperalgesia from toes to mid-calf. There was a 1.7<sup>0</sup> difference between his left and right leg with the left cooler. His right leg was completely normal in colour and sensations.

With his eyes closed he perceived that his left knee was twice the size of his right, his left ankle slightly enlarged and his toes larger than the rest of his left foot. When he was touched with a cotton bud below his left patella, he complained of feeling the same sensation on the plantar aspect of his left foot in the region of his MTP joints (Fig.4.2c). A similar sensation was felt again in his left knee when the same region of his foot was touched. He was unable to differentiate between light touch and pinprick; both evoked the same feeling of 'discomfort'. The sensations were not present when the subject viewed the examiner touching his limb or when vibration was used.

Throughout this subject's three week inpatient stay the referred sensations could be elicited. Although his mobility had marginally improved on

discharge, his pain continued at the same level and his left knee remained swollen.

#### **4.3.4 Case 4**

A 41 year old woman was referred to the outpatient department with a seven year history of pain in her right foot following a Wilson's Osteotomy. She had had delayed healing post surgery which had required an extended period of immobilisation and, despite tricyclic antidepressant therapy and multiple episodes of physiotherapy, she had experienced persistent pain, primarily around her right MTP joints ever since. On presentation she described a throbbing pain which extended beyond the site of initial injury and was exacerbated by weight bearing. She had allodynia, hyperalgesia in her right foot and dysaesthesia on the lower third of her right shin. There was swelling around her MTPs and a temperature difference of 0.8<sup>0</sup> C between her right and left lower legs with her right cooler.

With her eyes closed she perceived her right knee and ankle to feel 'heavier' than her left and her right foot to be twice the size of her left. When she was touched with a cotton bud on the sole of her right foot, under her MTPs, she reported feeling the same sensation in her right calf. When light touch was applied to the anterior of her right knee, in the patellar tendon area, this was referred distally to the dorsum of her right foot (Fig 4.2d). The same sensations were evoked with a neurotip but not perceived as sharp in the referral site. Vibration was not referred and all referred sensations were lost when she viewed the area being touched.

Over the next six months this woman received a novel treatment of mirror visual feedback (McCabe et al., 2003; see Chapter five) and was reviewed monthly. Her pain reduced from 6/10 at rest to 1.7/10 as measured by a visual analogue scale and the perceived excessive swelling of her right foot diminished. The referred sensations found on presentation could not be re-evoked at any of her follow-up appointments.

#### **4.3.5 Case 5**

A 57 year old woman was referred with a four year history of CRPS affecting her left hand and was admitted for rehabilitation. The condition had occurred spontaneously and persisted despite nerve blocks, physiotherapy, acupuncture and Gabapentin. She had fixed flexion deformities of the fingers on her left hand with an extended index finger and complained of intermittent dystonia. Her hand was swollen with allodynia and hyperalgesia present from her fingertips to elbow. Thermal imaging showed a  $1.6^{\circ}$  difference between the right and left forearms with the left cooler.

With her eyes closed she described her left hand, from her fingertips to wrist, as feeling tight and larger than the right. When a cotton bud touched her left upper arm she felt a pulling on her left ear (Fig 4.2e). This sensation was felt again when she was touched on the left shoulder but, in addition, she now reported that she felt her left thumb, fingers and wrist were also being touched. The referred sensation in her hand increased her pain at rest, from 5/10 to 8/10 on a verbal ten point scale and her fingers involuntarily became more clawed. When the cotton bud was moved away from her shoulder the sensations in both her ear and hand disappeared, the pain gradually diminished and her fingers relaxed. The referred sensations in the left thumb, fingers and wrist were re-evoked when the left cheek was touched (Fig 4.2f). Pinprick evoked the same sensations as light touch at all of the above mentioned referral sites but was not perceived as sharp. Vibration was not referred. When the subject viewed her limbs and face being touched, with the aid of a mirror, she reported a tightening in her left fingers but this was to a lesser extent than when she had her eyes closed. Her hand did not become clawed and her pain levels remained at pre-examination levels. The referred sensation of pulling on her left ear and touch on her left hand, were not present with vision.

This woman's condition remained unchanged throughout her two week inpatient stay and the referred sensations remained constant.

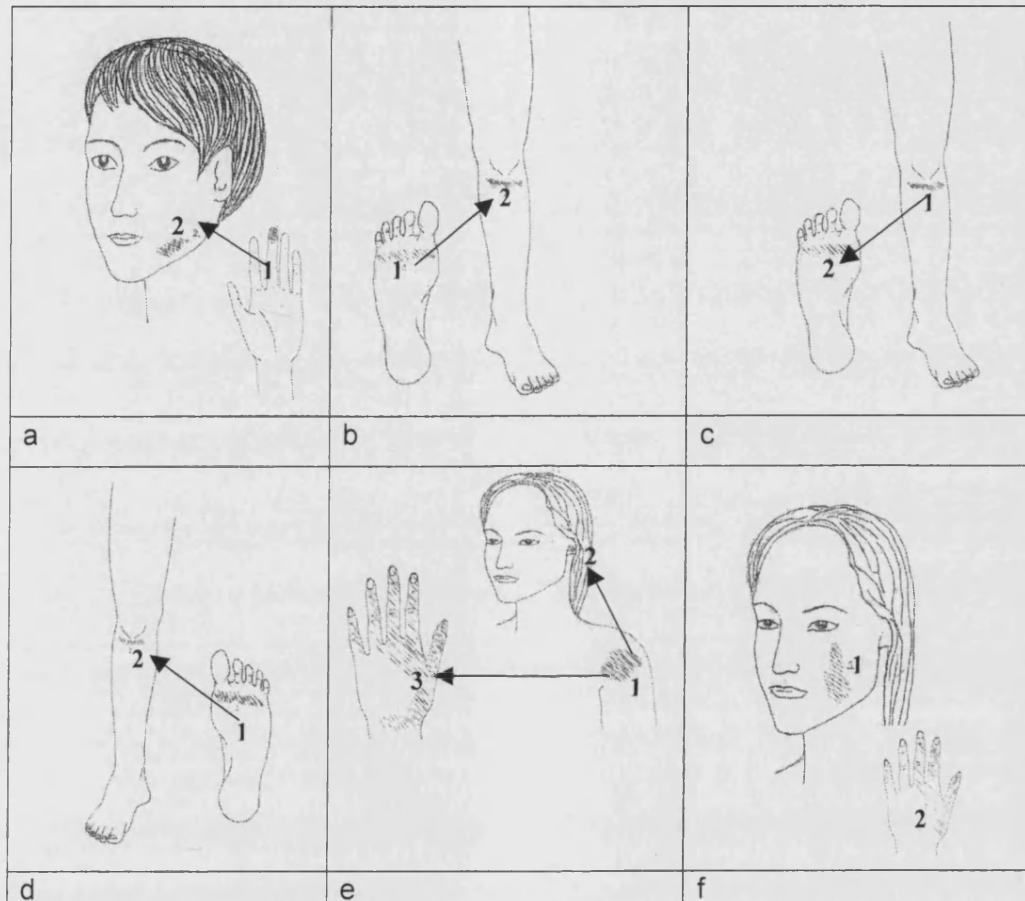
#### **4.3.6 Summary**

All patients reported referred sensations during examination with their eyes closed. They were experienced in real time and disappeared when



stimulation ceased or vision was permitted. When the subjects viewed the area being touched the sensations were either diminished (Case 5) or not present, and when the symptoms of CRPS resolved (Cases 1, 2 & 4), referred sensations were lost. Sensations were referred in a modality specific manner, with touch referred in all cases and pinprick also referred in two (Cases 1 & 2). Vibration was never referred. All referred sites were located on body parts immediately adjacent, on Penfield's homunculus, to the stimulated site.

**Figures 4.2a-f** Artists' impression of Cases 1-5 illustrating location of stimulus and direction of referred sensations (area touched =1, referred site/s = 2,3). a) to d) correspond to Cases 1 to 4; e) & f) correspond to Case 5. Shaded area (1) depicts area stimulated by examiner, shaded areas 2 & 3 depict where referred sensations were felt. The arrows illustrate direction of referral.



#### 4.4 Discussion

This is the first report of referred sensations in CRPS. The novelty of this finding may be due to clinicians not expecting such anomalous sensations or failing to see the potential significance when patients reported them. In addition, examining patients with their eyes closed is not routine clinical practice in rheumatology. Light touch was the main sensation referred and this fits well with reports of referred sensations in other conditions (Ramachandran and Hirstein, 1998; Turton and Butler, 2001). When these sensations are present in amputees touch is typically the modality referred, with vibration, pinprick, temperature and stroking sensations less so (Ramachandran et al., 1992).

Light touch is perceived when A $\beta$  fibres (large myelinated) are stimulated, though in CRPS A $\beta$  fibre stimulation has been found to elicit the experience of pain (Torebjork, 1990). Vibration however, is also transmitted by A $\beta$  fibres, but referral of this modality was not found in this patient sample. Interestingly, Rommel et al. (2001) showed an increase in the touch threshold on the ipsilateral side of the CRPS affected limb using quantitative sensory testing. They concluded that as this deficit extended beyond the area affected by CRPS, it was unlikely that systematic damage was occurring at the primary afferents, and this was more likely to be due to changes in processing within the central nervous system. In this study I also found that only those with early CRPS (<8 weeks) felt pinprick referred sensations. This may relate to Rommel et al.'s finding that those with significantly longer disease duration had a higher incidence of generalised sensory deficits (2001). However, it is difficult to state conclusively the significance of this result in the light of the small sample size.

The locations of the referred sites in this study population are consistent with previous reports in other pain conditions (Ramachandran et al., 1992; Flor et al., 1997), and fit particularly well with predicted cortical changes that have been shown to occur within the somatosensory body map (Halligan et al., 1993). Ramachandran and Hirstein (1998) proposed that due to the location and speed with which referred sensations occur in amputees, such "ectopic representations" following functional remapping were probably due to the unmasking of latent synapses within the cortex, as previously described in

primates (DeFelipe et al., 1986; Jones, 1990). These synapses are suppressed when there is simultaneous input from two connected receptors, but with reduced or impaired sensory activation in one area, the connection becomes disinhibited. Recent imaging studies using magnetoencephalography in six patients with upper limb CRPS Type 1, have also shown changes in the cortical somatosensory map, though it was not reported whether these were associated with referred sensations (Juottonen et al., 2002). There was a significantly shorter distance between the areas representing the thumb and little finger on the somatosensory cortex contralateral to the affected limb than the ipsilateral side. Interestingly, there was no significant correlation between the distance of thumb and finger, and the level or duration of pain. However, a more recent imaging study on twelve subjects with CRPS type 1, did show that evidence of mechanical hyperalgesia in the affected limb was a good predictor of cortical reorganisation (Maihöfner et al., 2003). There was also a significant correlation between levels of pain and cortical reorganisation, with those reporting higher levels of pain demonstrating a greater shift of the hand area to the limb on the cortical sensory map. Again, referred sensations were not explicitly sought in this study.

Alternatively, referral of sensations may occur at the spinal level. A large body of evidence shows that sensitisation of wide dynamic range neurons at level V of the dorsal horn, results in ipsilateral and contralateral enlarged receptive fields which do not rely on a cortical homunculus (Ji and Woolf, 2001). In addition, experimental models of peripheral neuropathic pain all demonstrate bilateral spinal cord changes after unilateral nerve damage (Koltzenberg et al., 1999). However, all of the patients in this study had CRPS 1 so, therefore had no precipitating major neural trauma. Their sensations were not referred bilaterally, either from the stimulated site to its contralateral partner (i.e. left hand to right hand), or mirrored on the contralateral side (i.e. from stimulated site to referral site on the unaffected limb). In addition, the speed of referral both in terms of disease duration, response time on stimulation, and resolution as the condition improved; combined with the magnitude of the sensations all detract from a purely spinal route. As we have seen in Chapter two, recent thinking is that CRPS is a disorder that involves both CNS and peripheral nervous system

components (Baron et al., 2002; Jänig and Baron, 2002); therefore isolating one clear route for referred sensations is at present problematical.

The reason for the reduction of sensory input in amputees is clear, but in CRPS where the affected limbs are hypersensitive, one may expect there to be greater sensory input. One explanation is that in CRPS we are seeing a pathological increase in sensory input from one area and hence encroachment of adjacent brain parts following the relocation of the limb's representation in the sensory map, as suggested by the recent imaging studies (Juottonen, 2002). Another proposed theory is that the excessive sensory input from the painful area of the affected limb results in a decreased perception of other sensory input from the remaining half of the body, resulting in a functional 'neglect-syndrome' as demonstrated by a hemisensory deficit (Rommel et al., 1999). Conversely, it is possible that the considerable sensory dysfunction within the peripheral parts of the painful limb is registered as a loss, and the adjacent areas on the Penfield homunculus, now encroach. Whichever scenario occurs, the findings from these five case reports show that the processes underlying referred sensations are reversible over a short period of time. Moreover, these processes do not produce referred sensations in the presence of normal sensory or direct visual feedback. The finding of bi-directional referred sensations is particularly novel (Cases 2 & 3), and would be impossible to demonstrate in amputees (where the condition is clearly irreversible).

Visual feedback strongly influenced the experience of RS. This concurs with the recent work conducted on amputees with phantom limb pain (Hunter et al., 2003). This showed that mislocalisation of sensations were most prevalent when the subjects' eyes were closed, and disappeared when the examined limb was being viewed. Touch and vision are inextricably linked. Touch is known to influence vision, such as dispelling the visual illusion of a 3 dimensional object when it is drawn on a flat surface. Equally, in some clinical conditions such as somatosensory loss after stroke, visual feedback of the affected limb during testing can significantly improve reported perception (Halligan et al., 1997). In addition, recent findings by Taylor-Clark et al. (2002) showed the enhancing effect of vision modulated somatosensory cortical processing. Gregory (1998) points out that vision evolved from the simpler processes for touch, and that it is

possible the somatosensory map is inverted - (the feet above the hand) - in order to correspond with the inverted visual image on the retina. This ensures that the link between vision and touch is as short as possible. Consequently, when the subjects in this study viewed their limbs being stimulated, it would appear that the more powerful sense of vision overruled the referred sensations.

The incidence of referred sensations in CRPS is unknown, but in this cross-sectional study they were shown to be present in approximately a third of the total study population. It is difficult to establish how this compares to referred sensations in amputees as the literature focuses on case studies where the symptoms are present, rather than larger population based surveys (Ramachandran et al., 1992; Halligan, 1993). However, anecdotal accounts suggest that they are not present in all amputees, and that even when they are this may not be a constant finding. Further work on larger populations is now required to try to identify any factors that may contribute to the existence of referred sensations in CRPS, and whether their presence is significant to the course of the individual's disease. There were no apparent differences in this study between those who did experience them and those who did not.

In conclusion, the existence of referred sensations in patients with CRPS Type 1 provides evidence of associated central sensory plasticity resulting in or from impairment to peripheral neural systems. As was seen in the review of CRPS (Chapter two), this has important implications on understanding the pathophysiology of this disease, and explaining the connection between peripheral and central mechanisms. We will now go on to see how this knowledge can also help with the design of appropriate therapeutic interventions.

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## **CHAPTER FIVE**

### **A controlled pilot study of the utility of mirror visual feedback in the treatment of Complex Regional Pain Syndrome (Type 1)**

(Appendix 9; McCabe et al., 2003)

#### **5.1 Introduction**

The previous chapters have shown that the traditional view of a hard-wired pathway for the mechanism of pain is no longer considered appropriate and that pain arises from a complex interaction between psychological and physiological changes (Chapter one). One such change may include the influence of cortical remapping, and this we have seen is evident both clinically and via imaging, in both CRPS and amputee phantom limb pain, two conditions which share many similar characteristics (Chapters one, two and four). Another commonality between these two chronic pain disorders, is that treatment options are limited, with little evidence to support their efficacy (see Chapter two for CRPS). However, recent studies on subjects with phantom limb pain (PLP) have reported the analgesic benefits of mirror visual feedback therapy (Ramachandran and Roger-Ramachandran, 1996). This Chapter will report the use of this technique in patients with CRPS Type 1.

Ramachandran and Roger-Ramachandran (1996) proposed that PLP results from a disruption of the normal interaction between motor intention to move the limb and the absence of appropriate sensory (proprioceptive) feedback. They speculated that visual feedback might interrupt this pathological cycle (Ramachandran and Roger-Ramachandran, 1996). Using a mirror that enabled amputees to superimpose the visual image of their normal limbs on the location where they felt their phantom limb to exist, the authors found that the phantom spasms and their associated pain were rapidly relieved in 6 out of 12 cases during exercises involving the “virtual limb”. As we have seen in Chapter one, Harris (1999) subsequently hypothesised on the basis of clinical observation and functional imaging studies, that disorganised cortical representations may lead to the experience of peripheral pain. He proposed that a mismatch between motor intention and predicted proprioceptive, or visual feedback of the affected limb may drive this process (Harris, 1999).

Due to the similarities between PLP and CRPS, I hypothesised that the pain of CRPS is a consequence of disruption of central sensory processing, and that congruent visual feedback from the moving unaffected limb as provided by a mirror, would restore the integrity of cortical processing. Thereby relieving pain and restoring function in the affected limb.

## **5.2 Method**

### **5.2.1 Participants**

#### **Inclusion/exclusion criteria**

See Chapter three for recruitment procedure, inclusion/exclusion criteria and ethical considerations.

### **5.2.2 Clinical method**

Subjects were assessed at two time points: on presentation and six weeks later. These time periods were selected to fit in with routine clinical care so as to minimise inconvenience to the subjects. The assessment protocol was divided into three distinct stages, two control phases (using no device and viewing a non-reflective surface) and an intervention phase (viewing a mirror). An additional daily diary was used to record frequency of mirror usage and an average weekly count was calculated from the total number of entries per week so that a trend in mirror use could be identified. It was important that subjects recorded these details daily to ensure accuracy of data collection, as this can be lost when a retrospective methodology is used (Skevington, 1995). However, diary records were considered 'complimentary' to the main data collection points (weeks one and six), as non-completion is a recognised problem with this methodology particularly over an extended period (Bowling, 1997).

Visual Analogue Scales (VAS) assessed pain intensity with 0 = 'no pain' and 10 = 'pain as bad as it could be' as the end anchor points on a 10cm horizontal line. This method of data collection was selected, as it is easily understood by subjects and reliably measures changes in pain (Oppenheim, 1992). By using an end-anchored scale there was a risk that subjects may be drawn to mark the extreme ends (Streiner and Norman, 1999). However, in reality, studies have shown that there is little difference in subject rating

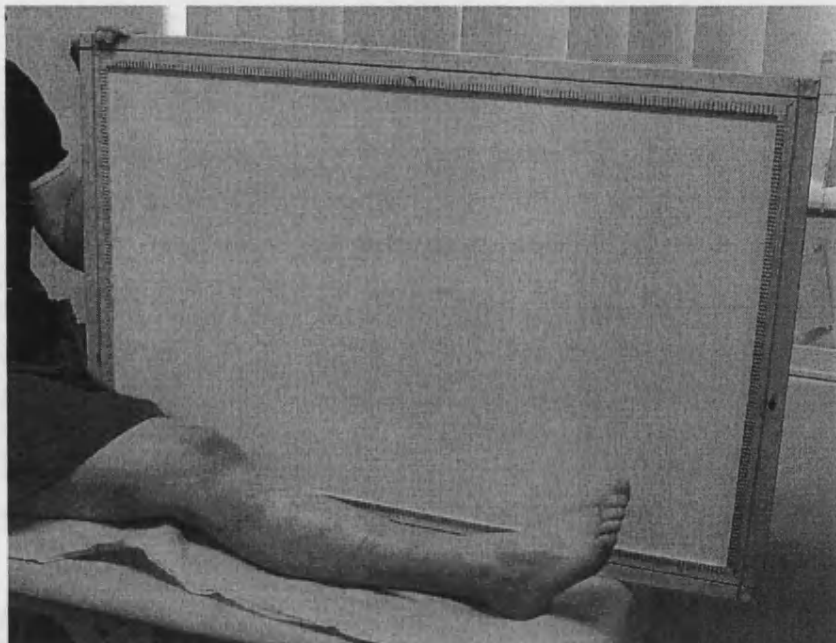
between end-anchored scales and those which use adjectives, equally spaced along the scale (Dixon et al., 1984). The uni-dimensional nature of VAS may be restrictive in some studies but pain intensity only was required in this study, rather than the particular sensory qualities of that pain, and therefore it was considered an appropriate methodology. Subjects were asked to mark the VAS to indicate the severity of their pain at rest and on movement. It was considered important to measure both, as movement commonly exacerbates the pain of CRPS (see Chapter two).

InfraRed Thermography (IRT) was used to quantify vasomotor changes that influenced temperature in the affected and unaffected limbs (Uematsu, 1988). This method of assessment is well recognised in CRPS (see Chapter two) and standard clinical practice at the Royal National Hospital for Rheumatic Diseases. It detects near surface blood flow and is a highly sensitive method which does not require physical contact with the patient. This is particularly important when the imaged area may be intensely painful as in CRPS. The resulting images are digitally processed and present a pattern of temperature distribution. A difference  $\geq 0.4^{\circ}\text{C}$  is considered significant (Uematsu, 1988). Images were taken on presentation and at week six.

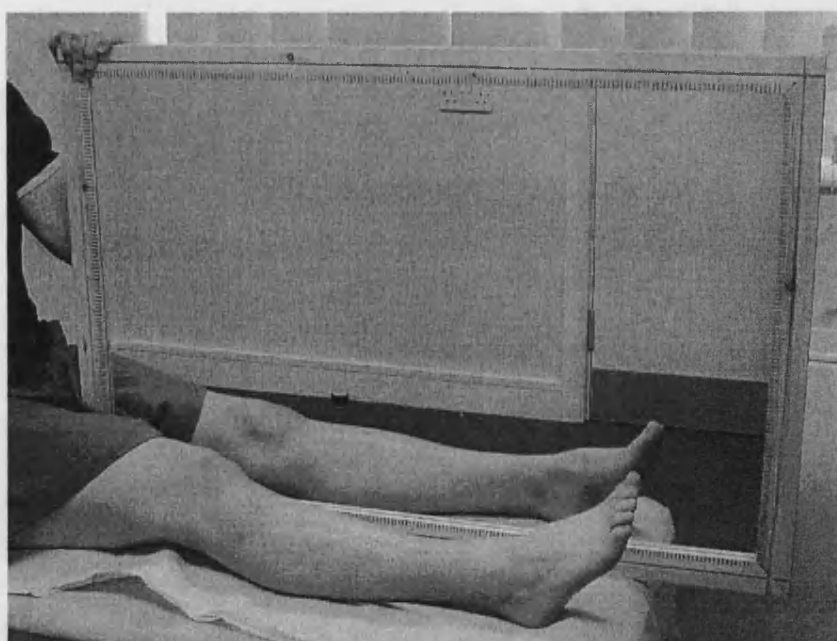
Subjects were seated and initially asked to visualise both limbs (affected and unaffected). Pain at rest and on movement was recorded (Control Phase 1). A non-reflective board was then positioned perpendicular to the subject's midline with the unaffected limb facing the non-reflective surface and the affected limb hidden (Control Phase 2). Subjects were asked to attend to the non-reflective surface for a period of five minutes and exercise their non-painful limb and, if possible, their painful limb in a congruent manner (Fig.5.1a). All subjects were asked to attempt to perform similar exercises - flexion / extension cycles of the relevant body parts. These exercises were demonstrated by myself and then rehearsed by each subject in my presence to ensure uniformity

**Fig 5.1**

**a)** Subject viewing non-reflective surface with painful limb hidden.



**b)** Subject viewing non-painful limb in mirror with painful limb hidden.



across the study group. The range of movement and speed of these exercises was dictated by the subjects' pain. Following the control stages, a mirror of similar size to the control device was positioned so that only the unaffected limb and its reflected image in the mirror, could now be seen (Fig.5.1b). Subjects attended to the reflection now occupying the space of their painful limb. Again subjects were requested to exercise both limbs (flexion / extension cycles as described above) for a period of five minutes, in a congruent manner. Pain on movement was recorded after each control and intervention stage.

Following the initial procedures, subjects were directed to use the mirror as frequently as they wished. No firm guidance on frequency was given as there were no specific data on this issue in the PLP study (Ramachandran and Roger-Ramachandran, 1996) and therefore a completely exploratory approach was taken. However, a maximum time limit of ten minutes was set for each period of mirror therapy to ensure concentration was maintained. Subjects were also advised to conduct the treatment protocol in a quiet environment, where concentration would not be interrupted. Subjects recorded daily the frequency of their mirror usage.

### **5.3 Results (table 5.1)**

Eight subjects were recruited aged 24-40 years (mean 33 years) with disease duration of 3 weeks to 3 years (three subjects early disease  $\leq 8$  weeks, two intermediate, 5 months and 1 year, and the remaining three long standing disease of  $\geq 2$  years). CRPS was precipitated by trauma in four of the eight subjects (Cases 3,5,7 & 8), with no obvious precipitate identified in the remaining four. Case 6 had a concurrent diagnosis of Ankylosing Spondylitis but there was no clinical or imaging evidence of synovitis or enthesopathy in the painful region. Case 7 had extensive ulcers on the affected limb, and all three chronic cases (6-8) had contracture deformities in the CRPS affected limb due to prolonged immobility.

**Table 5.1 Patients characteristics and the effect of the control and intervention phases on their pain at presentation; the frequency of mirror use on follow-up and final pain scores at 6 weeks with infra-red thermal temperature differences between affected and unaffected limbs.**

At presentation							Follow up								
Subject (painful limb)	Symptom duration	* Mean temp. difference (°C) [non-painful - painful limb]	Control Phase 1 Looking at both limbs (No device)		Control Phase 2 Painful limb hidden	Intervention	Freq. Mirror usage x per day (Duration of each treatment 10 mins.)						At 6 weeks		
			Pain VAS at rest	Pain VAS on movement	Pain VAS on movement	Pain VAS on movement	Week						Pain VAS	Mean temp. difference (°C)	Treatment duration (weeks)
							1	2	3	4	5	6			
Case 1 (left leg) 38yrs F	6 weeks	1.1	9	9	9	2	8	3	3	3	2	0	0	0.2	6
Case 2 (left arm) 28yrs F	3 weeks	2.0	7	8	8	3	4	4	3	3	2	0	0	0.4	6
Case 3 (left leg) 34 yrs F	8 weeks	2.7	6	8	8	2	9	4	3	0	0	0	0	0.8	4
Case 4 (right arm) 35yrs F	5 mths	1.9	0	5**	5**	3**	5	4	5	4	5	4	2**	0.3	6
Case 5 (right arm) 40yrs F	1 year	0.5	4	6	6	6	5	4	5	4	4	3	1	0.4	6
Case 6 (left leg) 24yrs M	2 years	1.4	7	8	8	8	5	5	5	0	0	0	8	1.3	Unresolved
Case 7 (left leg) 38yrs F	3 years	Not performed***	4	5	5	5	4	4	0	0	0	0	5	Not performed	Unresolved
Case 8 (left leg) 27 yrs M	2 years	2.1	7	8	8	8	4	4	0	0	0	0	8	2.6	Unresolved

\*Region of interest constant Significant difference if >0.4°C.

\*\* Stiffness

\*\*\* Case 5 had widespread ulceration on her left leg which made thermal image interpretation impossible.



All presented with a single limb affected by allodynia, hyperalgesia, reduced movement with related pain and stiffness, and vasomotor disturbances. The only exception to this was Case 4, who reported severe stiffness of the limb with little pain on movement, but met all other criteria. There were no apparent differences at presentation in pain on movement between the three disease duration groups. The small sample size and non-randomised participant selection ruled out any formal statistical analysis (e.g. comparison of means) on this data and all other numerical data described in the results

All subjects had had previous interventions that did not relieve pain, including analgesia, physiotherapy modalities, sympathetic blocks, immobilisation, TENS, Osteopathy and acupuncture (table 5.2). The more chronic cases had received the greater number of interventions, which included sympathetic blocks and immobilisation. Standard physiotherapy treatment was continued throughout the study period (table 5.3) for all subjects except Case 5, who had discontinued treatment prior to the start of the study due to lack of benefit. The analgesic type, dose and frequency remained constant from pre-study to throughout the study period for those with chronic disease (Case 6-8). However, all Cases from 1-5 reduced their analgesic requirements as the study progressed, and at the six week follow up only Case 5 was still requiring any form of analgesia, and this only on an intermittent basis.

### **5.3.1 Control stage**

All subjects reported no relief of pain on movement when both limbs were visualised without a device or when the non-reflective surface was viewed. Indeed, movement exacerbated pain, as is commonly found in CRPS (see Chapter two). Control phase 2 of the protocol (using a whiteboard in place of the mirror) was only performed at the initial assessment. The reason for this was that participants, who experienced an immediate analgesic response with the mirror, were aware that the white board trials were purely for control purposes. Therefore it no longer worked as a fair control and in addition, as the mirror was so clearly beneficial to these participants, they were reluctant to continue with its use. In order to keep the protocol uniform across the study participants, this phase was dropped for the six week assessment.

**Table 5.2 Therapeutic interventions prior to mirror visual feedback**

Subject	Analgesia	IRSB (G)*	Physiotherapy modalities	Occupational therapy	Immobilisation	TENS	Osteopathy	Acupuncture
Case 1	NSAID <sup>1</sup> Simple		√					
Case 2	NSAID Compound		√	√				
Case 3	Compound		√					
Case 4	NSAID		√				√	
Case 5	Compound		√		√			
Case 6	Opioid	√	√					√
Case 7	Opioid	√	√		√	√		
Case 8	NSAID	√	√		√			

\*Intravenous Regional Sympathetic Blockade (Guanethidine) <sup>1</sup> Non-steroidal Anti-Inflammatory Drug

**Table 5.3 Treatment received during study protocol in addition to mirror visual feedback**

Subject	Analgesia	Physiotherapy modalities	Occupational therapy	Osteopath
Case 1	Simple	√		
Case 2	NSAID	√	√	
Case 3	Compound	√		
Case 4	None	√		√
Case 5	Compound			
Case 6	Opioid	√		
Case 7	Opioid	√		
Case 8	NSAID	√		

### **5.3.2 Intervention stage**

All three subjects with early CRPS ( $\leq 8$  weeks) reported a striking reduction in their pain VAS during and after visual feedback of their moving unaffected limb as provided by the mirror. A marked analgesic effect was observed within a few minutes of mirror usage, followed by an abrupt return of pain when the mirror was removed initially. With repeated usage (4 – 9 x daily, week 1), the period of analgesia progressively extended from a few minutes to hours, requiring less mirror use over the six week study period. At six weeks there was a reversal of vasomotor changes as measured by IRT, a return to normal function and no pain at rest or on movement. All three subjects felt they no longer required analgesic relief from the mirror and had stopped prior to assessment at six weeks (Case 3, week 4, Cases 1 and 2, week 6).

The two subjects with intermediate disease duration, 5 months and 1 year, (Cases 4 & 5) reported that the mirror immediately eased their movement related stiffness, but there was no analgesic effect in Case 5. They both reported that this reduction in stiffness facilitated movement and the effect lasted for increasing periods after mirror usage. Although no objective data was collected on function, both subjects felt that by six weeks function had improved to such an extent that they were able to return to their usual manual occupations. Interestingly, despite the lack of analgesic effect during the mirror visual feedback procedure, Case 5 reported reduced pain at the 6 week follow-up (VAS 6/10 at presentation to 1/10 at 6 weeks). Reversal of IRT temperature differences were recorded in Case 4 at 6 weeks and Case 5 remained with no significant difference between the two affected limbs.

No subjective relief of pain and stiffness or reversal of IRT temperature differences were observed in the three subjects with chronic disease ( $\geq 2$  years) and they had all discontinued mirror usage by the end of week 3 due to lack of effect.

### **5.4 Discussion**

These observations are the first of their kind in CRPS and suggest that congruent visual feedback of the moving unaffected limb via a mirror, significantly reduces the perception of pain in early CRPS (Type 1), and

stiffness in the intermediated stages of the disease. The extent of the analgesic effect surprised both the patients and myself. The abrupt return of pain and stiffness when the mirror was removed supports the view that it was conclusively able to influence these sensations. The two internal control stages excluded an analgesic effect from: 1) moving the affected limb with normal visual feedback alone, and 2) the influence of selective attention when the limb was hidden. A placebo response is therefore highly unlikely, given the above control stages and the lack of benefit in chronic CRPS subjects. The effect was consistent between the five less chronic subjects, and repeatable within subjects. Extended use of the mirror provided increasing periods of analgesia, which aided compliance with exercise regimens. Whilst early CRPS can resolve spontaneously (approximately 50% of cases), I am unaware of any therapeutic manoeuvres or drug effects that can achieve such an immediate analgesic effect. In addition, when the intervention is stopped there is an abrupt return of pain. This emulates almost exactly the findings with PLP patients (Ramachandran and Roger-Ramachandran, 1996). Mirror Visual Feedback appears to be a simple, inexpensive and, most importantly, a patient directed treatment. The ability to self-regulate one's own health has been shown to be important to people (Carver and Scheier, 1982; Hyland, 1987), particularly when pain is being managed; hence the development and success of patient controlled analgesic systems (Curry et al., 1994). Mirror visual feedback would also meet that need for patient controlled therapy.

These results support the hypothesis that the CNS is capable of generating a feedback dependant state that can produce pathological levels of pain. In CRPS, this might involve a mismatch between different interdependent modalities, such as a disruption of normal interaction between motor intention and sensory feedback, as suggested by Harris for other intractable pain states (Harris, 1999; see Chapter one). In those with an inherent vulnerability to this incongruence, it can lead in some, to referred intractable pain following trauma or in others, promote CRPS with a central nervous system origin. This might explain why some types of CRPS occur without discrete peripheral injury. This theory of individual vulnerability will be explored further in the next chapter.

The subjects' pain and stiffness signalled by this incongruence, can be corrected by the use of false, but nevertheless congruent, visual feedback of the unaffected limb. The mirror reflection permits the subject to rehearse and practice movements of the affected limb, without having to directly activate those parts of maladaptive central processes that typically produce pain. The centrally processed visual input which appears to originate from the dysfunctional and painful side, acts to re-establish the normal pain free relationship between sensory feedback and motor intention, and consequently results in the rapid resolution of the pain state. In the absence of mirror feedback, movement exacerbates the pain, as was demonstrated in the control stages. In the subjects with long-standing disease there are two possible reasons why mirror visual feedback was ineffective. The first was that trophic changes such as contractures limited movement, and the second that neural pathways may be more established over time. This finding has been recently corroborated by research on the use of imagined hand movements in CRPS where a strong relationship was found between duration of CRPS and average response times for subjects to visualise imagined movements that matched pictures of hand positions (Moseley, 2003). Interestingly, what also influenced response times were the subjects' perceptions of pain to achieve each manoeuvre. The more awkward the hand position in the picture, the slower the response times. Schwoebel et al., (2001) have demonstrated a similar finding in their motor-imagery study with CRPS patients. One possible explanation for these variations in response is that a guarding type mechanism comes in to play, which operates at the higher levels of motor processing (Moseley, 2004), perhaps within the motor intent or motor planning stages, and this slows or prevents movements. It is conceivable that the sensitivity of this guarding mechanism increases with disease duration, and hence the findings in these studies.

The effect in the two intermediate cases, where the easing of stiffness was more apparent than an analgesic response, provides further evidence that time plays a part in this process. Interestingly, Single Photon Emission Computed Tomography studies (Fukumoto et al., 1999) have shown that the early stages of the illness are associated with increased blood flow in the thalamus, while in the later stages this region shows hypo-perfusion. These

changes and the peripheral changes that occur over time, may also explain the lack of treatment effect in subjects with chronic CRPS, and the more limited effect in the intermediate cases. Clearly the reliability of these findings need to be tested in a larger study population to confirm their reproducibility and to verify precisely what effect the chronicity of disease has upon the effectiveness of this therapy.

In summary, this exploratory study has shown that pain, without apparent nociceptive input, can be alleviated when corrective sensory input is provided in some subjects with CRPS. The logical extension of this finding must therefore be that pain can be generated, in the absence of neural trauma, when sensory input is distorted. This argument will be tested in the next chapter.

## 5.5 References

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## **CHAPTER SIX**

### **Simulating sensory-motor incongruence in healthy volunteers: implications for a cortical model of pain.**

#### **6.1 Introduction**

We have seen that pain can be alleviated in some patients with CRPS and PLP when corrective sensory input is provided, and the implications of this finding have been briefly discussed in relation to pain mechanism theories and the sensorimotor system (Chapters one, two and five). Up until now this thesis has concentrated on subjects who are experiencing chronic pain but now we will explore whether a disruption between motor output and sensory input can induce pain in healthy volunteers. If proven, this would demonstrate conclusively that pain can be generated without nociceptive input and, those 'incomprehensible symptoms of pain and other sensory disturbances' seen in some Rheumatology patients (as described in Chapter one), can start to be explained.

In addition to the phantom limb literature (Ramachandran and Rogers-Ramachandran, 1996; Ramachandran et.al., 1992), and my own data on CRPS (McCabe et al., 2003a; McCabe et al., 2003b), it is now apparent that the central nervous system (CNS) may be critical in generating a feedback dependent state, which can result in pathological sensations in some patients, independent of their initial peripheral pathology. A review of recent clinical and experimental work indicates that evidence for this conclusion comes from several sources:

1. association of pain following changes in cortical limb representation after non-traumatic repetitive movements (Elbert et al., 1995, Byl and Melnick, 1997)
2. reports of stiffness typical of pre-amputation Rheumatoid arthritis (RA) in the phantom limbs of amputees with RA (Haigh et. al., 2003).

3. the influence of pain on the body schema as demonstrated by: slower response times when individuals with upper limb, unilateral CRPS mentally rotated their painful limb compared to their unaffected one (Schwoebel et.al., 2001); neglect-like symptoms in CRPS (Galer and Jensen, 1999).

4. evidence of central reorganisation in chronic pain conditions (Flor et. al., 1997, Elbert et.al., 1998).

The findings from these and other studies can be best summarised using Harris' (1999) hypothesis, which states that conflict between motor intention, proprioception and vision may elicit "cortical pain" in the same way "that incongruence between vestibular and visual sensation results in motion sickness". Thus far most studies have understandably examined patients, many with longstanding clinical conditions, where it is difficult to establish the effect of secondary or initial peripheral changes. However, one way to show how this mismatch between sensory and motor systems could produce clinical symptomology is to experimentally generate the mismatch and examine the effects in healthy volunteers.

Fink et al. (1999) provided some preliminary evidence for this somatosensory symptomology using PET imaging with healthy volunteers. They studied the effects of performing in- and out-of-phase motor co-ordination tasks whilst viewing the reflected image of one limb in a mirror and then without the mirror. All 10 subjects were asked to rate the strangeness/peculiarity of their experience on a scale ranging from 0–9 (0 meaning not at all, and 9 meaning extremely peculiar or strange). The subjects' ratings confirmed that the critical condition was when out-of-phase movements were performed whilst viewing the mirror image of a single limb, thereby creating incongruent visual feedback. In this condition subjects rated their feeling of peculiarity as  $3.5 \pm 2.6$  (mean  $\pm$  SD), a statistically significant difference ( $P < 0.05$ ) when compared with peculiarity of  $0.8 \pm 0.9$  where there was no mirror and all movements were in-phase.

On the basis of Fink et al's (1999) preliminary findings, and the growing clinical and experimental evidence described above, I hypothesised that formal

evidence for the genesis of nociception-free pain would be found when sensory/motor conflict is generated in healthy individuals. This Chapter presents details of a two-phase assessment involving healthy volunteers, who moved their upper and lower limbs whilst undergoing normal and altered visual sensory feedback as provided via a mirror. The range of sensations they experienced was captured using a qualitative methodology.

## **6.2 Method**

### **6.2.1 Participants**

See Chapter three for general recruitment procedures, informed consent and other ethical considerations.

Forty one subjects were recruited over a one-year period. Subjects were informed that the purpose of their involvement was to collect comparative data for a study exploring the effect of altered sensory feedback on limb position sense (proprioception) in rheumatology patients. The rationale provided indicated that people with arthritic joints may have more problems accurately positioning their limbs than healthy subjects. The subjects were informed that when movements were performed they might transiently be associated with “some strange sensations”, but these should not be painful. This met the criteria for informed consent as outlined by the approving ethics committee (see Chapter three re- ‘ethical considerations’). A telephone contact was also offered post intervention for any subject who may have had concerns regarding continued presence of sensory disturbances. Demographic details and a brief medical history (including hand dominance) were collected on all subjects to ensure that inclusion and exclusion criteria were satisfied.

### **6.2.2 Clinical method**

The assessment apparatus was built to match that of Fink et al.'s (1999), but needed some modification so that both lower and upper limbs could be assessed, (Fink et al., explored the effect of visual distortion on upper limb movement only). It therefore comprised a metal frame, which supported a double sided board, one side (the intervention side) had a mirror attached and the other (the control side) a whiteboard. The whiteboard was considered an appropriate control as it ensured the limb behind it was hidden from view, (as

when the mirror was used), but there was no reflective image from the visible limb and therefore sensory feedback was not being deliberately distorted. The board containing the mirror/whiteboard could be moved up or down a central supporting pillar, and pivoted so that the mirror or whiteboard could be positioned on the left or right hand side and be adjusted for upper and lower limb assessment. Its size was such that when it was positioned between the subject's mid-line one limb could be obscured from view (figs 6.1-8).

Assessment of the effects was conducted in two phases both of which included bilateral upper and lower limb assessments. Phase one involved subjects viewing the control side (whiteboard condition) and moving their limbs congruently and incongruently (see figures 6.1 & 6.2; 6.5 & 6.6) and phase two involved the same movements being performed but this time the subject viewed the intervention (mirror condition) side (see figures 6.3 & 6.4; 6.7 & 6.8). The order of this assessment was kept constant with the control stage always occurring first followed by the intervention. This method was considered appropriate, as I was concerned that if sensations were generated in the intervention stage these may 'carry over' to the control stage as the assessment was continuous.

Prior to undergoing assessment, participants were asked to remove any identifying jewellery and articles of clothing on the parts of the limbs involved (e.g. watch, shoes, socks). This ensured that when the subject viewed the reflected image in the mirror it appeared similar to the hidden limb behind the apparatus. Subjects were seated on a couch, with the mirror/whiteboard in front of them positioned at right angles to the subject's body (fig. 6.1). All subjects were requested to put one limb either side of the whiteboard until they were in a comfortable position, but critically could not see the limb on the other side. For lower limb assessments the couch was raised so that the feet did not touch the floor to ensure that no additional sensory cues about their hidden limb's position could be gained, such as through touching the floor. A horizontal line was drawn on the mirror and whiteboard surfaces, which was level with the participant's umbilicus (upper limb assessment) or the great toe when the leg was fully extended and the ankle flexed (lower limb). A reference point on the subject's body was selected over one marked on the test apparatus to accommodate

variation in height between subjects. All participants were asked to flex and extend both arms in a congruent manner from the elbow (or legs from the knees) whilst attending to the horizontal line on the whiteboard side for a timed 20-second period (figs 6.1 & 6.5). Fink et al., (1999) did not state the duration of movements in their protocol but 20 seconds was chosen as an appropriate length of time as I was concerned that muscle fatigue may influence my findings with a longer period of exercise. Only the limb adjacent to the whiteboard could be seen throughout this assessment, the board hid the contralateral limb. The request to attend to a reference point on the whiteboard was included to ensure that attention was maintained during the short focused assessments. At the end of the 20 seconds, subjects were asked to position both hands (or feet) level with the reference point in the horizontal plane and with palms (soles) downwards. As subjects were only able to view one limb, the hidden limb had to be placed at the same perceived height as the visible one. Subjects were then asked a series of open questions: "How did that feel?" followed by a further prompt "Were you aware of any changes in either limb?" No specific, direct enquiry was made about possible sensory changes so that the subjects were not lead by the researcher, thereby eliminating a possible source of bias. Where painful sensations were reported the subjects were asked to rate these on a verbal rating scale where 0 = no pain and 10 = the worst possible pain. This scale is a modified Likert scale (Likert, 1952), which has been shown to reliably measure changes in pain (Oppenheim, 1992). A verbal rather than written scale was selected to minimise interruptions in the procedure and thereby aid the subject's concentration and recall skills.

The mirror/whiteboard was then pivoted, so that the contralateral limb could be assessed in the same manner as above, and the procedure repeated until the effect on each limb had been assessed whilst performing congruent and incongruent movements, first viewing the whiteboard and then the mirror. Upper and lower limb assessments were conducted consecutively and the order randomised between subjects.

**Figures 6.1- 8.**

Subject viewing the whiteboard (6.1 & 6.2; 6.5 & 6.6) and mirror (6.3 & 6.4; 6.7 & 6.8) whilst performing upper limb congruent (1 & 3) and incongruent (6.2 & 6.4) movements and lower limb congruent (6.5 & 6.7) and incongruent (6.6 & 6.8) movements.



Fig 6.1



Fig 6.2

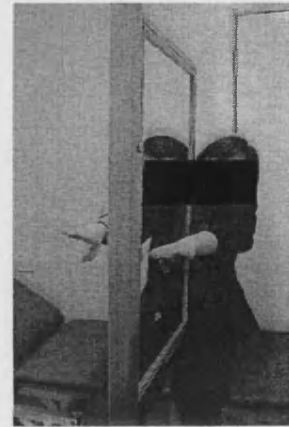


Fig 6.3



Fig 6.4



Fig 6.5



Fig 6.6



Fig 6.7



Fig 6.8

### **6.3 Data analysis and management**

Qualitative data, generated from the subjects' responses to the open questions were tabulated on MS-Excel and analysed using content analysis (Holsti, 1968; Frankfort-Nachmias and Nachmias, 1992; Bowling, 1997). Subjects were each allocated a unique code and the responses to the open questions were typed against the individual's code under the relevant stage in the protocol. Colour coding was used to indicate categories and sub-categories within emerging themes. The frequency of report of a particular sensation was totalled for each stage of the protocol. Quantitative data relating to the verbal rating scales for pain severity were stored and analysed on SPSS. These were tabulated against each individual's code for the relevant stage in the protocol. No statistical analysis was performed on this quantitative data as the sample size was inadequate. It simply provided an insight into the intensity of the sensation experienced by an individual.

### **6.4 Results (table 6.1)**

The results of the forty-one subjects (9 males, 32 females) aged from 23-65 years (mean 40.2 yrs SD 10.4) with the majority right hand dominant ( $n=38$ ), were that twenty-seven (66%) subjects reported sensory changes at some stage in the protocol; 14 describing no effect. The frequency and range of symptoms reported varied across the study population, with some appearing more vulnerable to the triggering of these symptoms than others. Table 1 shows the study population categorised into five groups of varying levels of vulnerability to sensory disturbances. This has been based upon subjects' frequency of symptom reports. Therefore, high vulnerability = sensory disturbances at all stages of the protocol, moderate vulnerability = sensory disturbances in all intervention stages + one control stage, mild vulnerability = sensory disturbances in all intervention stages but none in the control stages, minimum vulnerability = sensory changes in only one intervention stage and none in control stages, and no discernible vulnerability = no reported sensory changes at any stage of the protocol.

Subjects reported discomfort, changes in temperature and/or weight, perceived additional or lost limbs, and disorientation. Altered sensations were described predominantly in the hidden limb though this sometimes automatically

conferred sensations on to the visualised limb, such as the hidden limb felt heavier, and therefore the visualised limb was perceived as lighter. All altered sensations faded rapidly after limb movement had ceased and the hidden limb could be directly visualised by the subject. Detailed descriptions of each perceived sensation are reported below, with the phase that they occurred in the protocol in brackets (control =subject viewing whiteboard, intervention = subject viewing mirror).

#### **6.4.1 Types of sensory changes reported**

##### **6.4.1.1 Discomfort to mild pain**

The phenomenological descriptions included under this theme ranged from a “tingly sensation” and “pins and needles”, to an “ache”, “slight pain” or “shooting pain”. During the control phases one subject (subject ‘A’) reported that they felt a “light, tingling sensation” in their left lower arm (right hand dominant) as they performed congruent and incongruent movements with their left arm hidden from view. When the mirror image of the limb was viewed, this tingly sensation was again described “Fairly quickly my left arm felt tingly from the fingertips to elbow” (incongruent intervention, subject ‘A’), and “I felt a tingling in my right hand” (congruent intervention, subject ‘B’). An aching sensation was also described: “I felt a slight achy feeling in my right arm” (incongruent intervention, subject ‘J’), and pins and needles: “The left arm became numb with pins and needles” (congruent intervention, subject ‘A’) and “I had pins and needles in both feet” (incongruent intervention, right lower limb hidden, subject ‘C’). Others reported a definite pain “I wanted to rest both legs as they felt....slightly painful.” (incongruent intervention, left lower limb hidden, subject ‘D’), and: “There was a little bit of pain in my left hand, shooting down from the elbow” (congruent intervention, subject D). All subjects quantified their pain as  $\leq 2/10$  on a verbal rating scale.

##### **6.4.1.2 Temperature change**

A change in temperature in the hidden limb was reported when incongruent movement was performed whilst subjects viewed the mirror image of one limb. One subject described their limbs becoming warmer: “...both hands felt quite hot” (left upper limb hidden, subject ‘D’) and another cooler “..my right



foot felt cold" (subject 'B'). The researcher found no obvious difference in temperature to touch.

#### **6.4.1.3 Weight change**

Subjects' hidden limbs were perceived as either becoming heavier or lighter, and this sometimes conferred a perceived change in weight on the visualised limb. When attention was focused on the whiteboard one subject reported that there was "a bit of heaviness in both elbows" (congruent control, left upper limb hidden, subject 'D'), and another that "the right hand felt a lot lighter", (hidden limb, congruent control, subject 'B'). When the mirror image of a limb was attended to, subject 'D' still experienced the increased weight of their elbows (congruent intervention), and subject 'B' now reported "My right foot felt very light at the end of the exercise" (congruent and incongruent intervention). This reduction in weight was also described as "a slightly floaty sensation in my left arm" (congruent intervention, subject 'E'), and "my right arm was floating so I was not sure precisely where it was" (incongruent intervention, subject 'G'). For one subject the perceived increase in weight of their hidden limb impeded their movement so that at the end of the exercise "The left arm felt so heavy I was unable to lift it to the same height as the right" (incongruent intervention, subject 'B').

#### **6.4.1.4 Perceived loss of or additional limbs**

The visual illusion created by the mirror of having one arm visible, one "in the mirror" and another concealed behind it produced in some subjects a feeling that they had "lost a limb", and others that they had a "third" one. The most distal end of the moving hidden limb was always affected when these sensations were experienced, but the degree to which the remainder of the limb was involved varied between individuals. However, even during the control stages subjects reported a loss of sensation in the hidden limb. Subject 'A' stated that they were "less aware of the right hand" (congruent control), and subject 'B' had "less sensation in the right hand.....no idea where the right foot was" (congruent control). "The left foot felt as if it wasn't there from the mid-calf down" and "I had no idea where my right foot was" (subject 'B' incongruent control). This loss of limb was so real to subject 'I', "I had no idea where my left

foot was" (congruent control) that they had problems locating their foot when the exercise was complete, and found it difficult to bring it to the reference mark.

When the mirror was viewed, this report of perceived loss of limb was described as "took a second to find my right hand" (congruent intervention subject 'K'), "I had a delayed reaction to where my right hand was" (congruent intervention subject 'L'), "...left arm was no longer present" (incongruent intervention subject 'E'), and " ..it took a second to find my right hand.....I lost my right leg.....the left leg disappeared" (incongruent movement subject 'K'). Normal perception of the affected area returned rapidly when the limb was either visualised or touched by the subject.

Conversely, some subjects experienced the perception of an additional limb: "I felt I had three hands" (incongruent intervention subject 'M'), "I felt I had two right hands and my real one was drifting off" (incongruent intervention subject 'D'), "I feel I have three legs" (incongruent intervention subject 'N'). Again this illusion was quickly dismissed once movement stopped.

**Table 6.1 Details of individuals' characteristics showing type of protocol induced symptoms experienced in relation to stage in the protocol, limb affected, and individual vulnerability.**

**Key to sensation experienced:** P =pain/discomfort, T= temperature change, W =weight change, LOL = perceived loss of limb, EXL = perceived extra limb, PEC = feelings of peculiarity  
**Key to hidden limb affected:** LUL =Left upper limb, RUL = Right upper limb, LLL = Left lower limb, RLL = right lower limb

Study ID	Gender	Dominant hand	Whiteboard		Mirror	
			Congruent movement	Incongruent movement	Congruent movement	Incongruent movement
High vulnerabilities						
A	F	R	P (LUL)  LOL (RUL)	P(LUL)  PEC (LLL)	P (LUL) LOL (LUL,RUL) PEC (RLL)	P (LUL, RUL) LOL (LUL,RUL,LLL,RLL) PEC (LLL,RLL)
B	F	R	W (RUL) LOL (RUL,RLL) PEC (LUL)	LOL (LLL,RLL) PEC (RUL)	P (RUL) W (RLL) LOL (LUL,RUL,LLL)	P (LUL) T (RLL) W (LUL,RUL,RLL) LOL (RUL,RLL) PEC (RLL)
I	F	R	LOL (LLL) PEC (RLL)	LOL (RUL) PEC (RLL)	LOL (RUL,RLL) PEC (LLL)	LOL (RUL,LLL) EXL (LLL)
Moderate vulnerabilities						
C	F	R	PEC (RLL)		P (LLL) PEC (RLL)	P (LLL,RLL) LOL (LLL,RLL) PEC (LUL)
D	F	L	W (RUL)		P (LUL) W(RUL) PEC (RLL)	P (LLL,RLL) T (LUL,RUL) W (LUL,RLL) EXL (LUL,RUL,LLL,RLL) PEC (LLL)
K	F	R	PEC (LUL)		LOL (RUL) PEC (RUL)	LOL (RUL,LLL,RLL)
Mild vulnerabilities						
E	F	R			P LUL) W (LUL) PEC (LUL,RUL,LLL,RLL)	W(LUL) LOL (LUL, RLL) PEC (LUL)
H	M	R			PEC (LUL)	W (LUL,RLL) EXL(LLL,RLL)
L	F	R			LOL (RUL) PEC (LUL)	EXL (LUL) PEC (RUL)
M	F	R			LOL (RUL) PEC (LLL)	EXL (LUL) PEC (RLL)
N	M	R			PEC (RLL)	EXL (RLL)
Q	M	R			PEC (RUL)	P (RUL) LOL (RUL,RLL)
S	F	R			LOL (RLL) PEC (LUL,RUL,RLL)	LOL (RLL) PEC (RUL)
W	F	R			PEC (LLL)	EXL (RUL,RLL)

Study ID	Gender	Dominant hand	Whiteboard		Mirror	
			Congruent movement	Incongruent movement	Congruent movement	Incongruent movement
Y	F	R			PEC (LUL,RLL)	PEC (RUL,LLL)
<b>Minimum vulnerables</b>						
F	F	R				W (LUL,RLL) LOL (LUL) PEC (RUL)
G	F	R				W (LUL,RUL) LOL (RUL) PEC (LLL,RLL)
J	M	R				P (RUL)
O	F	R				PEC (LUL)
P	F	L				PEC (LUL)
R	M	R			LOL (RUL,LLL) PEC (LLL)	
T	F	R				LOL (RLL)
U	M	R				EXL (RUL)
V	F	R				EXL (RUL)
Z	F	R			PEC (LUL)	
X	F	R	LOL (RUL)			
AA	F	R				PEC (RLL)

<b>No discernible vulnerability</b>						
BB	F	R				
CC	M	R				
DD	F	R				
EE	F	R				
FF	F	R				
GG	F	R				
HH	F	L				
II	F	R				
JJ	F	R				
KK	F	R				
LL	F	R				
MM	M	R				
NN	F	R				
OO	M	R				

#### **6.4.1.5 Feeling of peculiarity**

This category encompasses the type of experience reported by most of the subjects in the functional imaging study by Fink et al. (1999). Subjects in my study often reported a range of feelings in the non-seen hand and included such comments as “a bit odd” (control congruent subject ‘B’) “very weird” (congruent intervention ‘C’), “disliked it” (congruent intervention subject ‘K’), and “bizarre” (congruent intervention subject ‘E’).

For some, the visual effect generated the illusion that the reflected image was moving at a different pace to their hidden limb: “The leg in the mirror looks as if it is going slower because the real one is going in the opposite direction” (incongruent intervention subject ‘G’). Others found that the movement became “mechanical” (congruent intervention subject ‘I’), and they “had to really concentrate to keep the right leg moving in the opposite direction” (incongruent intervention subject ‘A’). Some experienced “a loss of control” (‘B’) and their leg movements “became wild” (incongruent intervention). “Nausea”, “confusion”, “dizziness” and “disorientation” were also described (subject ‘A’, ‘O’ & ‘P’, incongruent intervention).

#### **6.4.2 Frequency of report (table 6.2)**

Sensory changes were reported through all phases of the protocol : control (congruent movement n = 6, (15%) incongruent movement n = 4, (10%), and intervention (congruent movement n = 17, (41%), incongruent movement n = 27, 66%). The maximum number of reports of anomalous sensations occurred when the subjects moved their limbs incongruently but perceived, via mirror, that they were moving them congruently (incongruent movement n = 27, 66%). No inferences can be drawn from the influence of hand dominance, as the majority were right handed with only 3 out of the total study population (7.3%) left handed. These three were scattered across the different ‘vulnerability’ groups with one reporting sensations typical of the ‘moderate’ group, one typical of the ‘minimum’, and the third reporting no abnormal sensory disturbances.

**Table 6.2. Details of the incidence of symptoms reported at each stage of the protocol in relation to the total study population.**

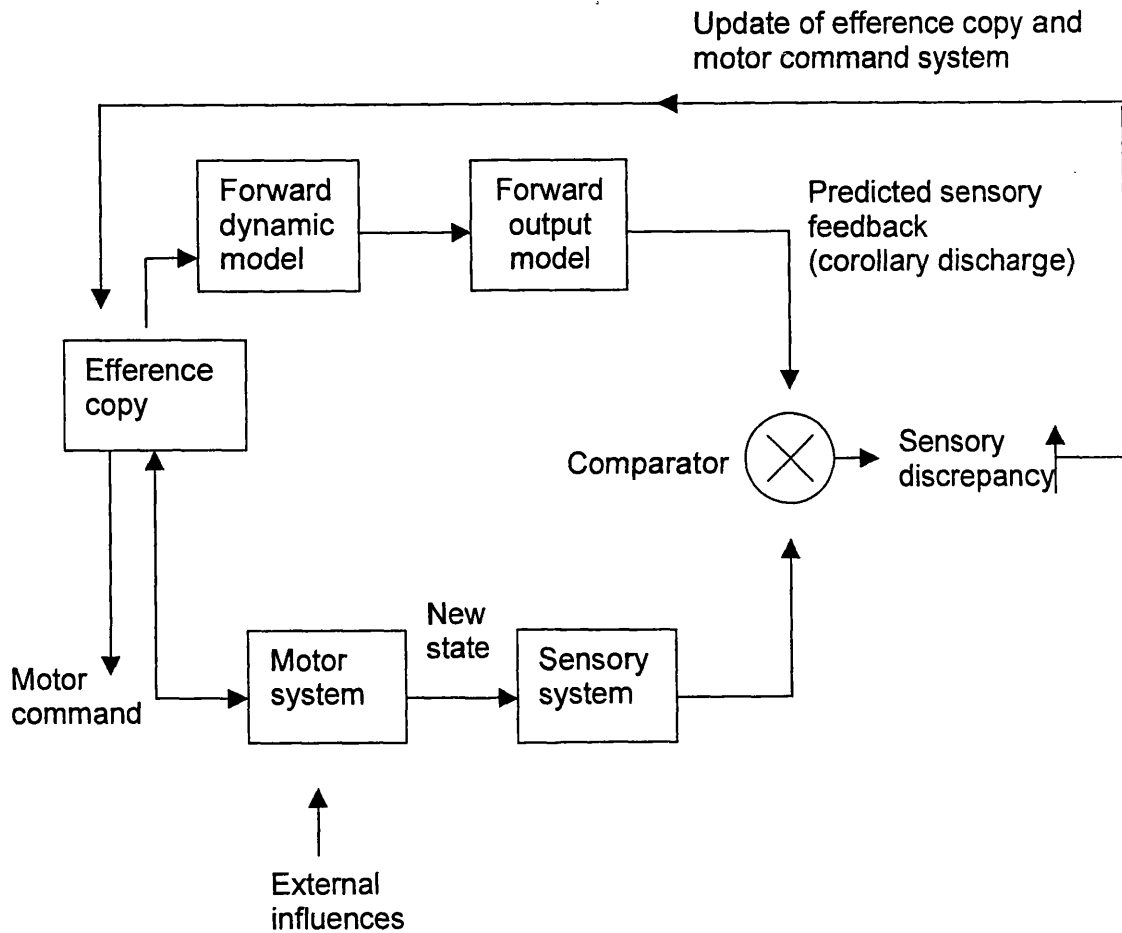
	Whiteboard		Mirror		At any stage in the protocol
	Congruent movement	Incongruent movement	Congruent movement	Incongruent movement	
Pain	1 (2%)	1 (2%)	5 (12%)	6 (15%)	7 (17%)
Temperature	0	0	0	2 (15%)	2 (15%)
Weight change	2 (5%)	0	3 (7%)	6 (15%)	6 (15%)
Perceived loss of limb	4 (10%)	2 (5%)	8 (20%)	11 (27%)	15 (37%)
Perceived extra limb	0	0	0	9 (22%)	9 (22%)
Peculiarity	3 (7%)	4 (10%)	16 (39%)	14 (34%)	22 (54%)
Total number of subjects experiencing any sensation	6 (15%)	4 (10%)	17 (41%)	24 (59%)	27 (66%)

## 6.5 Discussion

Following Harris's (1999) speculation that pathological pain may be cortical in origin, this is the first study in which motor and predicted somatosensory changes have been studied systematically in healthy volunteers. On the basis of these findings, I suggest that visually mediated changes between the motor, and predicted somatosensory feedback, was sufficient to produce the anomalous symptomatology reported by more than 60% of these normal subjects. More specifically, I would suggest that the primary cause lies within the motor control system, whose role is to manage the relationship between motor commands and sensory feedback.

When moving a normal limb, sensory information (derived from current state information including joint angles prior to the execution of a motor command) is crucial for deciding the type and extent of awareness we perceive for each specific movement. More importantly, such information is necessary when evaluating the expected or predicted consequences of those movements (Frith et al., 2000). Normally there is a continuous integration of sensory information as to the location of the target limb. This is provided by a "feed forward" system which predicts the sensory consequences of a motor command (see figure 6.9). This signal is then monitored directly by comparing the predicted movements with those of actual sensory feedback (Wolpert et al., 1995). Each time a motor command is issued to a limb, an "efference copy" of that motor command is produced in parallel, and it is this that provides the basis for predicting the consequences of the actual or planned movement (see Chapter one). Indeed in most cases, normal awareness and experience of our limb is often based on the predicted state rather than the actual state. If the system monitoring the actual feedback detects a deviation from that predicted (Frith et al., 2000), it will communicate this as a subjective experience, for example an over or undershoot in the case of pointing or grasping. We have seen that if sensory remapping has occurred, as in CRPS and phantom limb pain, then sensory information may be misrouted. When this occurs, pain is used to alert the system and individual that there is a conflict between motor and sensory systems. Likewise, when central monitoring mechanisms

**Figure 6.9** Schematic diagram depicting the role of the efference copy in the motor control system





detect a discordance between body position, balance and equilibrium then an experience of motion sickness is triggered.

These monitoring mechanisms can be triggered by externally produced conflict (e.g. incongruent movement whilst viewing the mirror), or internally (e.g. the ageing process leading to inaccurate execution of movement and/or altered proprioception, cortical re-mapping, or disease damage in RA resulting in stiffness (Haigh et. al., 2003). Harris (1999) has suggested that Repetitive Strain Injury is a form of pathological pain that can arise in some workers involved in repetitive tasks, such as typing where fine finger movements give little opportunity for discrete proprioceptive feedback, combined with 'on line' visual monitoring, thus generating sensory motor conflict.

The common feature for all these conditions is that the mismatch produces an anomalous experience -predominately pain - triggered by central systems designed to monitor and activate, when normally congruent sensorimotor systems are disrupted. Thus these feedback dependent states continue to trigger the monitoring mechanisms, and ultimately produce acute or chronic pain, either via duration or intensity. It is however possible that interventions can be targeted to correct this initial source of conflict, and restore the monitoring systems, thus preventing or alleviating pain. This was demonstrated in Chapter six where mirror visual feedback was shown to alleviate pain in those with CRPS (McCabe et. al., 2003a). In the case of motion sickness, the cessation of movement will alleviate symptoms.

I would therefore suggest that in CRPS, impaired efferent copies (either peripherally generated from protracted dysfunctional proprioceptive input, or centrally altered), leads to a prediction that intended or attempted movements of the limb will result in pain. This may be where Moseley's (2004) proposed 'guarding mechanism' is sited so that if a potentially painful movement is planned, albeit through motor-imagery, movement is slowed or even 'discouraged'. Since, as Frith et al. (2000) have argued, much of our conscious awareness of limb movements is largely derived from the predicted, rather than feedback from the peripheral joints themselves, the impaired efferent copy serves to activate brain mechanisms responsible for monitoring the effects of

motor intention. These in turn generate a qualitatively altered perception (dysaesthesia, paraesthesia and pain), on the basis of the impaired efferent information that is experienced, and reported as abnormal sensations by the patient.

The concept that a motor/sensory mismatch gives rise to anomalous sensations including pain, is new and thus far has found most of its evidence from the detailed study of patients with chronic pain. The results of this study provide additional support for the concept, in that many normal subjects (without clinical pathology) experienced a wide range of sensory disturbances, including localised pain, when exposed to transient motor/ sensory conflict. The speed with which these sensations were produced in this group of healthy volunteers was surprising given that the sensory disturbances were only the result of a 20-second exposure, with the majority occurring "almost immediately" the limb movement started. It was felt that to extend the time period may have distorted the results with additional symptoms starting to occur due to muscle fatigue, but it would not be difficult to envisage that a longer time frame would have increased the severity of symptoms for some, or perhaps induced abnormal sensory experiences in those who otherwise reported no change. Significantly, once normal visual input was restored, the anomalous sensations rapidly resolved and no subject took up my offer of telephone support to discuss any continued sensory disturbances.

It could be suggested that the majority of sensory disturbances were reported in the final stage of each assessment (incongruent visual feedback), because the subject was fatigued by this stage, or that the required posture generated sensory disturbances. However, the upper and lower limb assessments involved an equal amount of movement from both limbs during right and left limb assessments. In addition, these assessments were continuous and randomised. If fatigue and posture played a part then one would have seen a 'carry over' effect of symptoms into the control stages of the second limb assessment. For example, sensory disturbances reported during the last stage of a right upper limb assessment (incongruent movement, whilst viewing the mirror), would still be apparent at the next stage in the protocol, congruent movement of the left upper limb, whilst viewing the whiteboard. This

'carry over' effect was not seen, and the control stages always had the lowest report of sensory disturbances across the study population regardless of which limb was assessed first. This lack of 'carry over' of symptoms between the intervention and control stages, demonstrates that future studies could randomise the order of assessments without the data quality being compromised.

In retrospect an additional baseline assessment (congruent and incongruent limb movement without the whiteboard or mirror), would have been of benefit in this study. When the protocol was devised I considered the whiteboard to be an adequate control, as I had not envisaged simply hiding a limb from view would generate any sensory disturbances. This baseline assessment stage has now been added to other studies using this technique.

It is clear from these findings that some individuals are more prone to experience these anomalous sensations than others. Several explanations are possible. The most obvious is the brevity of the experimental procedure. In the real world such conflict of sensory / motor systems, whether as a result of external or internal factors, might be expected to take place over a much longer period, and be more gradual in onset. Another aspect worth considering is an individual's relative threshold for tolerating and coping with such conflict (as in the case of sea-sickness). The threshold for triggering such monitoring mechanisms is presumably biologically (genetic factors, age, gender, and sex hormone state) and contextually determined. Consequently there will be some who are more vulnerable than others. In this healthy volunteer study the 20 second exposure was sufficient to elicit anomalous experiences in some, but not all subjects. Within those that were more "vulnerable" to the experience, simply having one limb hidden from view was sufficient in six cases to generate sensory disturbances, whereas for others ( $n = 14$ ) nothing abnormal was reported, even when visual information conflicted with actual limb movement. Although sensory conflict is one of several potential sources responsible for triggering pain, it is not unreasonable to assume that those already experiencing chronic pain or peripheral minor injury might have a lower threshold, whereby minor anomalies could be experienced as more severe. Indeed Gracely et.al. (2002) using fMRI and subjective ratings in patients with

fibromyalgia, compared to those of healthy controls, found that applications of pressure deemed as painful by the patient group resulted in a greater number of active cortical regions in the patients, and no common regions of activation between the patients and healthy control group. Thus supporting the hypothesis that cortical or subcortical pain processing was augmented or amplified.

It should not be forgotten that pain was only one of the many symptoms evoked in this study. I therefore suggest that, dependent upon the degree of motor-sensory conflict, central sensorimotor monitoring systems become activated resulting in the generation of a broad range of somatic experienced symptomology. This monitoring system (possibly the frontal brain area found by Fink et al., (1999) in their PET study using a similar artificial, short term visual proprioceptive mechanism) may be one of several naturally occurring CNS systems capable of triggering symptoms, including pain, as a sort of primordial warning of the need to avoid or take action.

In conclusion, I suggest that dysfunctional proprioceptive sensory feedback, either generated in the peripheries or centrally, can result in plastic brain changes that over time can produce impaired "efference copies" of planned motor commands. Once activated by intention to move, monitoring systems designed to detect significant mismatches between motor intention and expected sensory feedback, are triggered, and for some, painful sensory consequences ensue. Larger population studies are now required to validate these findings and in particular explore other factors e.g. age, which may influence them.

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## CHAPTER SEVEN

### Discussion and future direction

This Chapter will summarise the novel findings of this thesis and discuss them initially in relation to their contribution to current pain theories, and then specifically to our understanding of pain in the rheumatic diseases. Finally, the clinical implications of this work, and the direction of future research will be considered.

#### 7.1 Discussion

In Chapter one we saw that Descarte's theory of a simple pain pathway, starting with receptors in the skin, and finishing with interpretation in the brain, no longer holds true. The experience of pain was shown to derive from both peripheral and central mechanisms (at the spinal and cortical level), and that it could be greatly influenced by an individual's current, and previous life experiences. However, these proposed mechanisms still focused primarily on the initial trigger for pain arising in the peripheries, and although we saw that the experience of pain can become detached from the originating injury via 'wind up', the concept of pain originating in the central system, without nociceptive damage, was considered conjecture.

Nevertheless, we saw in Chapter two, that dramatic disabling changes can occur at the peripheral and central level in the absence of nerve damage, with CRPS Type 1 being a clear example of this. The existence of referred sensations in this condition (Chapter four), further confirmed that central changes do occur, and that these are directly linked to the levels of pain, with the loss of referred sensations as pain diminished. This pain could also be modulated by the artificial provision of corrective sensory input; literally turned off and on when the mirror was provided and then removed (Chapter five). It is difficult to imagine any other type of therapeutic modality which can manipulate pain so strikingly. This finding confirmed that the sensorimotor system can influence the perception of pain and we saw in Chapter six that it can also generate pain. Although these last two studies were exploratory in nature with no random sampling of subjects, their findings are unique and must surely lend

credence to my initial hypothesis that pain in some rheumatic diseases, is cortical in origin.

### **7.1.1 Summary of novel findings**

- The existence of referred sensations in patients with CRPS type 1, providing evidence of associated central sensory plasticity.
- Central sensory plasticity occurs early in the disease and can be modulated by changes in clinical status as shown by the loss of referred sensations in those with resolving CRPS.
- Corrective sensory input can temporarily relieve the pain of CRPS type 1 in some patients, when used for brief periods, but when delivered over a longer period, it can provide a permanent analgesic benefit.
- Modulation of pain via such a technique provides clear evidence that at least some of the pain experienced in CRPS type 1, is directly attributable to a sensorimotor mismatch.
- Artificially generating a sensorimotor mismatch in healthy volunteers, will create abnormal sensory symptoms experienced in the peripheries (e.g. pins and needles) and centrally (e.g. disorientation).
- Sensory symptoms, including pain, can be generated cortically without nociceptive input.

### **7.1.2 A cortical model of pain**

My research studies have shown that it is the interaction between the motor and sensory systems, managed by the motor control system, which is key to this proposed cortical model of pain. The environment, the musculoskeletal system and sensory receptors, all influence the transformation of motor commands to their sensory consequences (Wolpert et al., 1995). These sensations in turn influence the subsequent motor commands. Therefore a feed forward and feedback system is constantly in action, and it is at the interaction between the two, where actual sensory input meets the predicted sensory input, or efference copy, that sensory disturbances may be generated.



In order to be effective, the motor control system has to maintain a broad over view of the body's current state via the 'state variables' (e.g. joint position sense, body schema), but also work at the lower local level, to know exactly which muscles are required to deliver a specific movement. The manner in which a movement is conducted may have a multitude of different options, and therefore the higher and lower levels must interact in order to deliver the optimum method i.e. the most efficient (Wolpert et al., 1995). Smoothness of movement has been proposed as an ultimate aim of this system (Flash and Hogan, 1985), and recently it has been suggested that this is best achieved by unifying limb and eye movements (Harris and Wolpert, 1998). Harris and Wolpert (1998) propose that there is noise in the motor command, and that this is directly proportional to the size of the motor command. The larger the motor command required (i.e. the less smooth the movement), the greater the noise. With information based on predictions from both the visual and motor system, smoothness of movement is enhanced. It may be that by deliberately distorting visual input through either hiding the limb from view as with the whiteboard, or deceiving the system with the mirror, smooth movement becomes more difficult to achieve, and therefore a larger motor command is required. Perhaps the subjects' reports of their movements becoming "mechanical" and requiring "greater concentration", when they performed incongruent movements with the mirror, were directly attributable to the requirement for a larger motor command. Likewise the subject may perceive the consequent increase in noise as "disorientating" and "confusing".

Two centres in the brain determine vision: an 'older', evolutionary centre situated in the brain stem which is involved with locating objects in the visual field, and a second 'newer' centre, situated in the thalamus (with further pathways leading into the parietal and temporal lobes), which performs the task of recognising objects. The two systems work concurrently so that the older centre detects objects within the visual field, and the eyes are moved to study it and interpret it using the higher, more evolved second centre (Ramachandran, 2003). It is only activity within the second pathway that occurs at the conscious level, and therefore the scanning of objects (in the older centre), occurs subconsciously, so that for example, you can perform two tasks at once whilst constantly being aware of any potential danger e.g. driving while conducting a

conversation (Ramachandran, 2003). Importantly, the older pathway projects to the parietal lobes of the brain; these are responsible for providing a spatial layout of the world. We know too that damage to the right parietal lobe will cause left sided neglect, where a person will ignore stimulus on their left side, including the limbs on that side (Schwoebel et al., 2002; Ramachandran, 2003), thereby altering their body schema. It may be that in the case of neglect in CRPS, this older visual system no longer detects the affected limb and because this occurs at the subconscious level, the subject is not aware of the gradual lack of attention to the limb unless the higher, conscious centre is alerted to it. Clinically subjects demonstrate this by ignoring their affected limb and only acknowledging it when encouraged by a clinician to make a conscious effort to focus upon it. We saw above, that the motor control system relies on such 'state variables' as the scanning of the body schema, to predict the consequences of motor output, and that accurate information is required to promote smooth movement. This distortion in body schema will provide inaccurate predictive data; hence the motor command becomes inefficient and noise increases. The limb becomes increasingly difficult to move as a greater motor command is required, and the sensory feedback diminishes still further. This reduces its detection by the older visual centre even more, so a destructive cycle begins. The rerouting of sensory input from the affected limb to other adjacent structures on the cortical map, as seen in referred sensations, may exacerbate this lack of detection still further. The mirror, in this setting acts as a reminder to the older, evolutionary visual centre that the affected limb needs to be reintroduced into the body schema, and through persistent use, this transformation occurs. Thus 'state variable' data becomes accurate, movement efficiency returns and the limb moves smoothly once more.

We saw in Chapter one that Patrick Wall (1999) proposed that the reason sensory events are analysed in terms of appropriate motor response is evolutionary, so that an individual can act promptly to any threat, seeking safety or preparing for action. I would propose that the capability to generate sensory abnormalities within this motor control system fits well within his theory. If one requirement of this system is to alert the individual to danger, then it must have a means to achieve this, and we know that pain can have a dramatic effect upon an individual's actions. I suggest that the milder sensory changes are an

early warning system alerting, the individual to abnormalities within information processing, but if these persist and the threat is perceived as greater, then ultimately pain will be produced. This generation of symptoms may not be innocuous, as we have seen in Chapter one. Changes in the peripheries can have dramatic effects, and I would suggest that they may in themselves start a cascade of events, such as influencing the autonomic and sympathetic nervous systems, or perhaps changes in endocrine activity. This may be how the central and peripheral changes are linked in CRPS.

The triggering abnormalities that initially alert the motor control system may be generated by any one of the three factors which influence it: the environment, the musculoskeletal system and sensory receptors. The mirror acted as an environmental influencer in the healthy volunteer study. However, one other factor has been shown to determine an individual's response to these alerts, and that is innate susceptibility. Not all individuals develop CRPS following wrist fracture, and not all the healthy individuals studied experienced sensory disturbances. It would appear that some individuals are more vulnerable, or simply better at detecting these sensations. Further work is required to identify exactly what these influencing factors may be.

It would appear therefore, that the motor control system acts as a central monitoring mechanism, maybe one of many such systems in the body and I would propose to term them as 'ominory' from the Latin word *ominor* meaning to prophesy, predict, foreboding (McCabe et al., 2004; Appendix 10). My studies have focused on the mechanism that monitors motor/sensory conflict, but a separate ominory mechanism could generate motion sickness when there is discordance between body position, balance and equilibrium. The key feature of these mechanisms is that when they are triggered, they generate sensory disturbances such as nausea with motion sickness, pain in a phantom limb and a multitude of unpleasant sensations in CRPS. These resultant states I have termed 'dissensory' from the Latin word *dissensio* meaning conflict, disagreement. These are feedback dependent states which will continue to trigger the ominory mechanism, and ultimately either via duration or intensity of this state, the subject will suffer pain. In this model the motor control system is constantly scanning for irregularities in information processing, and inevitably

discrepancies will occur throughout a normal day, such as when you step off a pavement unexpectedly, or 'miss' the last step on a flight of stairs. Sensory disturbances will be constantly generated, albeit perhaps at an unconscious level. However, there are those who are far more aware of changes in their bodies, and report recurrent multiple medical symptoms which have no organic cause. This somatisation may result from a reduced threshold to these normal sensory changes, and consequently subjects start to report them as abnormal symptoms. This may explain the constant flitting of symptoms in those with Fibromyalgia, who like the healthy volunteers, describe changes in body schema; mild, generalised pain; and changes in body temperature (Wolfe et al 1990; Staud et al 2001).

This thesis has primarily focused on the pain of CRPS, and briefly touched upon Fibromyalgia and rheumatoid arthritis (Chapter one), but the same ominous mechanism may apply to the pain of osteoarthritis (OA), and indeed, the development of pathological changes in the joint. Sharma et al (1997) and Pai et al (1997) have both shown that patients with unilateral knee OA have worse proprioception in their affected and unaffected joints than elderly controls. The fact that both knees have reduced proprioception even when only one is diseased, supports the theory of 'mirror imaging' across the body (Shenker et al., 2004). The abnormal proprioception in the contralateral knee will be sufficient to continually trigger the ominous mechanism and perpetuate the problem. The subsequent dys sensory state may explain the clinical observation that some individuals report high levels of pain, when only minimal changes suggestive of OA are seen on X-ray imaging. This continuous sensory imbalance in the contralateral knee, increases the risk of injury and ultimately of generating OA (Hurley 1997). If targeted exercise is used to improve proprioception, the initial trigger is removed and the ominous mechanism suppressed, thereby perhaps preventing the onset of OA. Interestingly, patients with OA often report in clinic that their pain is worse at night, and this may be a direct result of reduced corrective sensory input that occurs at this time of day, thereby exacerbating the dys sensory state. A darkened room diminishes visual feedback and immobilised limbs reduce proprioceptive input.

In conclusion, a mismatch between motor output and sensory input triggers a warning ominous mechanism, which generates the dissensory state. In this state, the individual may experience a range of sensory disturbances included within which may be pain.

## **7.2 Clinical implications and future direction**

We saw in Chapters one and two the clinical implications of patients presenting with a variety of different painful symptoms and how difficult it may be for the clinician to determine the cause of each. This work now proposes an explanation for pain, which arises without originating trauma, and perhaps a means of identifying those most at risk of generating such pain. This raises the possibility of targeting vulnerable individuals for preventive treatment and using new therapeutic modalities for those already in pain.

In order to identify vulnerable individuals, larger population studies now need to be conducted to validate the reliability of my findings. The healthy volunteer study needs to be repeated on specific categories of individuals to establish what factors influence a subject's vulnerability, e.g. male versus female, the influence of age and hormones. In addition, do those who are already experiencing chronic pain have an even lower threshold to these sensory disturbances? Work in these areas is already underway with data collection commenced from an elderly population  $\geq 60$  years, and a second cohort of those with Fibromyalgia (FMS). Early findings on the FMS population (Bodamyali et al., 2004; Appendix 11) suggest that they do experience sensory disturbances at a higher intensity and frequency than healthy volunteers in all stages of the protocol, and that these changes are greater than their baseline recordings (with neither whiteboard or mirror). In addition, a student project is planned which will assess the influence of hormones on the sensitivity to abnormal sensory disturbances, as generated via the mirror/whiteboard protocol. This study will involve healthy controls, and patients with Fibromyalgia, rheumatoid arthritis and osteoarthritis. Their hormonal status will be monitored over a two month period and compared to their sensory reports on the mirror/whiteboard protocol.

For those already in pain exciting opportunities now emerge. We have seen that CRPS is an extremely difficult condition to treat and that the best outcome is achieved with early detection and treatment. The mirror/whiteboard protocol provides a potential means of identifying those at risk of this condition, and thereby enabling early treatment to occur with mirror visual feedback and other modalities. This system is currently being tested on patients immediately post distal-wrist fracture, to establish its use as a predictor of CRPS compared with validated, more complex and time consuming measures. It may be possible too to use it in other clinical settings to determine what contribution, if any, the motor/control system plays in an individual's symptoms. I would envisage that this would be particularly useful when a patient presents with pain of no obvious cause. This pain could now be targeted with treatments, which will deliberately improve information processing, such as improving sensory input via Physiotherapy, desensitisation, regular corrective visual feedback or TENs, and massage. These treatments are not new, but previously their application to this type of pain lacked an evidence base, and a trial and error methodology would be applied. Further studies are now needed to establish what intensity and frequency of these types of treatments is required to correct imperfect efferent copies, and at what stage in a disease is the optimum time for an intervention. In my mirror visual feedback study those with early disease, and who used the mirror frequently gained the greatest analgesic benefit. It may be that with even higher levels of mirror use (and perhaps combined with motor imagery), those with chronic disease would also have seen an improvement in their symptoms.

The evidence of referred sensations in CRPS was based on clinical findings alone, with the assumption that the location of referral directly related to changes on the sensory cortex. Imaging studies have shown that these changes do occur, but referred sensations were not screened for in the study population (Juottonen, 2002). A study proposal, in collaboration with The University of Exeter, is currently being drawn up to use fMRI to assess what changes occur in the somatosensory cortex when patients with CRPS first present, and then undergo mirror visual feedback over a three month treatment period. Referred sensations will be tested for, and it will be of interest to see what percentage of patients describe these, how treatment influences them and how these relate to actual cortical changes as seen on imaging. In Chapter four

we saw that approximately a third of the study population reported referred sensations, and it may be that cortical changes occur in all patients but are simply not detectable at the clinical level in everyone.

The studies outlined above are just the start of looking at pain in a different way. It will require close collaboration across a range of different specialities to fully unravel how the generation of pain is linked to the motor control system, but for all those patients who had no obvious cause for their pain, and felt their symptoms were “disbelieved”, it offers hope that we may at last be able to relieve them of their pain.

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# **APPENDICES**

# **Appendix 1**

## Main article

# Pain mechanisms and the rheumatic diseases

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## Abstract

*Pain is the predominant complaint of those with a rheumatological condition. This paper provides a broad overview of the current theories on the mechanisms of pain, the structure of the nervous system, and how these may relate to the sometimes seemingly incomprehensible symptoms of pain and other sensory disturbances that some rheumatology patients describe. Three case histories relating to rheumatoid arthritis, osteoarthritis and fibromyalgia are used to illustrate how this knowledge can be applied to clinical practice.*

**Key words:** Pain, pain mechanisms, rheumatoid arthritis, osteoarthritis, fibromyalgia

## Introduction

Pain is a familiar sensation to us all, whether it is the sharp pain from a cut, the sting of a nettle or the nagging ache of a tooth. For the majority of us our experience of pain is in unconnected, resolvable incidents that are interspersed by lengthy pain-free periods. However, for those with a rheumatic disease their pain may be ever present. The character and intensity of that pain may vary depending on the cause and course of the disease and may even be influenced by diurnal patterns.

Traditionally we associate pain with injury but the chronic pain of fibromyalgia challenges this belief, and patients and clinicians alike may find it hard to understand how pain can apparently strike from nowhere. This paper provides a broad overview of the current theories on the mechanisms of pain, and three rheumatology case histories are used to illustrate how these may relate to the seemingly incomprehensible symptoms of pain and other sensory disturbances that patients with rheumatoid arthritis (RA), osteoarthritis (OA) or fibromyalgia syndrome (FMS) describe.

## What do we mean by pain?

The word pain is derived from the Latin word 'poena' meaning penalty and some people still believe that pain is due to some real or imagined misdemeanour. Pain is not a sensation that is ever felt alone; its emotional effects always accompany it. It is usually a negative experience involving both physical and mental processes but may serve as a survival mechanism whereby minor pain may ensure withdrawal from a potentially life-threatening scenario or enforce inactivity to ensure we take time to rest and heal (Melzack and Wall, 1996: 11).

The relationship between pain and injury is not always as expected. Melzack and Wall (1996: 3) describe how although the severity of an injury usually determines the intensity of the pain there are instances where an injury may be sustained but pain not experienced until some time later. Conversely, severe pain may be experienced in the absence of tissue damage or long after an injury has apparently healed. The complexity of the experience has taxed scientists in defining it with the focus in recent years primarily on tissue damage that produces the sensation of 'hurt' (Sternbach, 1968; Mountcastle, 1980). This then raises the questions, how do you define 'hurt', and what about pain that occurs in the absence of tissue damage? In 1979 (Merskey et al., 1979) the International Association for the Study of Pain defined pain as: 'An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.'

This was the first definition that recognized the emotional dimension of pain and that injury and pain may not always be linked. It also demonstrates that pain is a subjective event which relies on the sufferer 'describing' the experience. This acknowledgement that both physical and mental processes are involved has fuelled the search for a mechanism that creates a sensation from a sensory input and then interprets that message using our mental processes (Wall, 1999a: 22–38). A single mechanism, or pain centre, has proved elusive and our understanding of this complex system is still far from complete.

### **Pain mechanisms – past to present**

The traditional explanation for our perception of pain is based on the 'specificity theory' that was first described in 1664 by Descartes (Melzack and Wall, 1996: 150–1). Descartes proposed that a specific pain system conveys messages from pain receptors in the skin to the brain using a system rather like a bell at the end of a rope. The rope is pulled, i.e. the skin is damaged, the message goes down the 'rope' and the bell is rung, i.e. the brain is alerted.

This simple theory remained relatively unchanged until the 19th century when greater knowledge of anatomy and physiology began to emerge. What became apparent at this time was that the 'specificity theory' did not allow for all the other

associated sensations that combine to give an experience of pain. Descartes had not allowed for the psychological contributions of pain, such as the effect of past experience or the current situation. Scientists of the 19th century, namely Muller and von Frey (Boring, 1942), contributed greatly to our understanding of the physiological mechanism of pain but again no allowance was made for any psychological modulation of it. Muller recognized that it is the sensory nerves that are instrumental in the transmission of external information to the brain and von Frey described specific sensory spots on the skin that recognize touch, cold, warmth and pain.

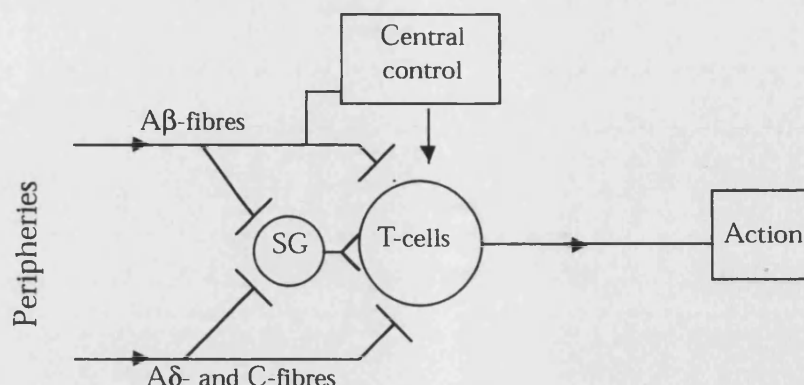
It was not until after 1965, following the publication of Ronald Melzack and Patrick Wall's gate control theory of pain (Melzack and Wall, 1965), that pain theories started to encompass the influence of psychological factors (Melzack and Casey, 1968). These theories succeeded in combining the existing knowledge of pain into a clear and concise theory on the nature of the experience of pain.

In order to fully understand Melzack and Wall's (1965) seminal work and how subsequent theories have built upon it, a brief review of the nervous system and its associated structures will be covered. For a more comprehensive overview the Textbook of Pain (Wall and Melzack, 1999) should be consulted.

### How do pain messages travel?

Sensory experiences are determined by a combination of the capacity of our nervous system to extract information from the stimuli that our bodies receive and the ability to process that neural input (Doubell et al., 1999). Our peripheral sensory nerves, comprising A $\beta$ - (fast, myelinated), A $\delta$ - (thinly myelinated) and C-fibres (slow, unmyelinated), perform the task of data gathering by transmitting information from the peripheries to the central nervous system. These highly specialized structures each transmit a unique signal to enable identification and differentiation of the stimuli. The A $\delta$ - and C-fibres are thought to be primarily responsible for the transmission of impulses associated with pain. The fast A $\delta$ -fibres transmit the sharp pain of an acute injury and the slower C-fibres produce the dull, aching pain of a deeper, more persistent injury and the burning quality of neuropathic pain. The sensations experienced when an ankle is sprained typify the subtle differences of these two types of fibres. Initially a sharp, precisely localized pain is experienced which rises rapidly in intensity but then falls away equally quickly (A $\delta$ -fibres). After this, a second, quite different pain is felt; it is deep, diffuse, poorly localized, steady and spreading (C-fibres).

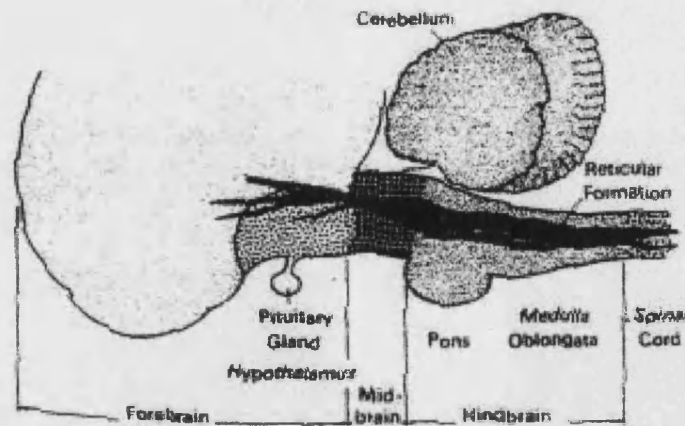
The first stage of information processing occurs at the dorsal horn in the spinal cord where these afferent sensory nerves terminate. Here, information from the peripheries is interpreted and acted on through interaction with the central nervous system (CNS). It is here that the gate control theory of pain comes into play.



**Figure 1:** Schematic diagram of the gate control theory of pain. Large ( $A\beta$ -fibres) and small diameter fibres project to the transmission cells (T-cells) and substantia gelatinosa (SG) in the dorsal horn of the spinal cord from the peripheries. The large fibres inhibit T-cell activity and the small fibres excite it. The inhibitory effect of the SG is increased by large fibre activity and suppressed by small fibre activity. Descending large diameter fibres from central mechanisms modulate this gate control system and influence the resulting action.

### Gate control theory (Figure 1)

When small diameter  $A\delta$ - and C-fibres are stimulated following injury, impulses are sent direct to the dorsal horn of the spinal cord where neurons, or transmission cells (T), are stimulated. These T-cells transmit information to the local reflex circuits and the brain but will be suppressed when there is increased activity of large  $A\beta$ -fibres. In addition to the T-cells there are also small cells in the substantia gelatinosa (SG) which have an inhibitory effect on the deeper dorsal horn neurons. Small fibre activity will suppress this inhibitory effect and large fibre activity excites it. This results in an accentuated effect on T-cell activity so that when small fibres are active, T-cells are stimulated and the SG is suppressed so that the 'gate opens' and messages pass to the brain to be perceived as pain. Conversely, when large fibres become active they excite the inhibitor of the SG and suppress T-cell activity thereby closing the gate (Melzack and Wall, 1996: 165–76). This explains why one's immediate instinct following injury is to rub the affected area as  $A\beta$ -fibres transmit the sensation of touch and therefore increased activity of these large fibres will decrease pain. Acupuncture and transcutaneous electrical nerve stimulation (TENS) are targeted to work on the same principle, through the excitation of large fibre activity.



**Figure 2:** Diagram showing the subdivisions (hindbrain, midbrain and forebrain) of the brain and the structures that lie within them. Reproduced with kind permission from Nathan P (1997) *General plan of the human brain*. In: *The Nervous System* (4th edn.) London: Whurr. Chapter 17, pp. 182–94.

Nerve impulses that descend from the brain further influence this spinal gating system. Large-diameter, rapidly conducting fibres activate selective cognitive processes, which in turn, by way of descending fibres, modulate the properties of the spinal gating system. When the output of the T-cells in the dorsal horn exceeds a critical level the action system is activated. This action system is what initiates the complex patterns of behaviour and experience that give rise to the distinctive nature of pain (Melzack and Wall, 1965). Exactly which areas of the brain are involved is the source of much debate and it could be argued that virtually all of the brain plays a role in the experience of pain; such is the complexity of the emotional and physical response. However, the brainstem, medulla, pons and midbrain are thought to be key players (Wall, 1999a: 39–57) and these areas in turn receive information from the cord and the forebrain (Figure 2). The limbic system (comprising hypothalamus, hippocampus, amygdala, septum and cingulum) and the reticular formation, sited in the midbrain, are considered to be particularly important for the behavioural and emotional responses to pain with the somatosensory cortex locating the site of the injury (Melzack and Wall, 1996: 122–45).

Endogenous narcotics, such as endorphins and enkephalins, are produced in the forebrain and midbrain. These also modulate the transmission of pain signals in the dorsal horn via the descending pathway. Serotonin is the major transmitter for these opioid-like substances and along with noradrenalin, it will trigger the release of these substances from spinal cord cells (Melzack and Wall, 1996: 122–45). Drugs such as



fluoxetine and amitriptyline, used for depression and some forms of pain, work by suppressing the re-uptake of these transmitters, thereby prolonging their action.

Whereas Descartes' theory proposes that people respond to pain by a simple cause-and-effect mechanism, we now understand that psychological processes, accessed via the descending pathway, modulate this effect. This modulation by cognitive processes explains, to some extent, how pain is more than a single sensation. It is an experience and one that may alter depending on an individual's previous and current life events.

### Peripheral and central sensitization

The gate theory of pain focuses primarily on how the CNS processes sensory information and it is portrayed as a somewhat hard-wired system. However, we now know that this is not the case. Neural circuits can reconfigure in response to external and/or internal stimuli. The acknowledgement that neural plasticity occurs is one of the major developments in current pain theory and its effect on the type and experience of pain may be significant. A persistent pain in the peripheries (such as chronic inflammation) can alter both peripheral and central signalling mechanisms.

Tissue damage incurred with a sprained ankle will result in a cascade of activities as chemicals are discharged into the area that surrounds the nerve endings. Mast cells release chemicals such as bradykinin, histamine and prostaglandins which either produce pain themselves or sensitize the nerve endings. The prostaglandins are particularly important as they dilate the blood vessels and make them leaky, resulting in the typical redness and swelling of injury (Melzack and Wall, 1996: 100). The mode of action of aspirin is to reduce the build up of prostaglandins.

The high thresholds of both A $\delta$ - and C-fibres ensure that they are normally only triggered by noxious stimuli. However, this threshold can be lowered when persistent stimulation occurs and these nociceptors (sensory receptors that react to painful stimuli) will start to fire on weak, non-noxious stimuli (Devor and Seltzer, 1999). This sensitization occurs in the peripheries (primary hyperalgesia) due to the release of chemical inflammatory mediators (e.g. substance P) into the skin from damaged C-fibres or as outlined above via tissue damage. Nerve fibres may also begin to fire spontaneously so that painful sensations are perceived even without stimulus. In addition, sensitization may occur centrally if nociceptor inputs persist (secondary hyperalgesia). With persistent stimulus from damaged tissue and nerves there is an increase in the activity of calcium channels within the spinal cord. These affect both pre-synaptic transmitter release and post-synaptic neuronal excitability (Dickenson, 2002). The drug gabapentin is a calcium antagonist and is therefore particularly appropriate for neuropathic pain. Active calcium channels increase the release of

glutamate, which is the key transmitter for afferent A- and C-fibres, and consequently increase the activity of glutamate receptors (e.g. N-methyl-D-aspartate, NMDA) that are implicated in wind-up and central sensitization (Dickenson, 1995). The findings of allodynia (pain due to normally innocuous stimuli) and hyperalgesia (increased response to normally painful stimuli) may be seen on clinical examination as this sensitization can result in a lowering of the A $\beta$ -fibre threshold so that touch now becomes a painful sensation.

In summary, when central sensitization occurs peripheral sensory neuron activity drives the central spinal systems and these in turn increase and prolong the incoming messages so that ultimately a dissociation occurs between the peripheral activity and the individual's experience of pain (Dickenson, 2002). This explains the apparent anomaly that when a nerve is cut pain is not reduced or stopped but actually exacerbated. A progressively damaged, hard-wired system would decrease in function but these are dynamic systems that fluctuate as circumstances change (Wall, 2000). Central and peripheral sensitization are thought to serve as protective mechanisms with the increase in pain ensuring that behaviour is adapted to limit further damage (Devor and Seltzer, 1999).

### Cortical remapping

With the advent of sophisticated imaging techniques objective evidence of neural plasticity at the cortical level has been widely reported in some chronic pain conditions (Ramachandran, 1993; Byl and Melnick, 1997; Elbert et al., 1998). These studies have shown changes on the somatosensory map following either an increase in sensory input, such as from the repetitive arm movements of professional musicians, or a decrease, e.g. deafferentation after limb amputation. Cortical areas that previously processed information from only one region have been shown to encroach on adjacent areas of the somatosensory map. For example, upper limb amputees were found to have sensory input from the face and upper arm invading the hand territory of the somatosensory cortex (Ramachandran, 1993). Clinical evidence of this remapping is evident in the observation of referred sensations in amputees (Ramachandran et al., 1992). This is when somatosensory feelings are perceived to emanate from a body part other than but in association with the body part being stimulated. These have also been found in patients with complex regional pain syndrome (McCabe et al., 2003a) thereby supporting the hypothesis that central mechanisms play a part in this chronic pain condition.

Recent thinking suggests that these cortical changes may not merely be a result of chronic pain but instrumental in the generation of it (Harris, 1999). Harris (1999) hypothesized that if there is conflict between motor intention, proprioception and vision then pain may be generated in the same manner that the

sensation of nausea is generated when vision and vestibular sensory inputs conflict in sea sickness. An example of this would be amputee phantom limb pain where motor output still perceives the limb to be present but proprioceptive and visual input is absent from the amputated area.

The role of the motor control system is to manage the relationship between motor commands and sensory feedback (Frith et al., 2000). This is to optimize the precision and efficacy of a movement as every movement results in an immediate sensory response. However, it is impossible to predict a sensory response purely from the motor commands and so the system relies on information known as 'state variables' (Frith et al., 2000). These include such things as joint angles and the current state of the system prior to the command being implemented. From an assimilation of this information the motor control system 'predicts' a certain response from the sensory system and 'controllers' within the system compare this desired state with the motor command required to achieve that state. The controllers then produce the appropriate motor commands to achieve the desired outcome. The prediction, or 'efference' copy, is often only a rough approximation of the actual consequences of a motor command but it is needed to: prepare the system for the consequences of that movement; assess performance if there is a delay in response; differentiate between internal and external influences on the system; and maintain a constant update on the interplay between sensory and motor systems. This prediction is then compared to that of actual sensory feedback and the current state of the system modified accordingly (Wolpert et al., 1995). The consequence of this chain of actions is that sensory events are analysed in terms of the appropriate motor response. Wall (1999b) suggests that there are three evolutionary explanations for this system. First, it enables an individual to remove the stimulus, second, adopt a posture to limit further injury and optimize recovery, and third, seek safety and a cure.

However, if cortical remapping has occurred, resulting in a misrouting of sensory information, then errors will occur in the above system. In the case of an amputee the predictor will continue to send motor commands and anticipate an expected sensory response but sensory feedback from the amputated limb is no longer possible and indeed information concerning that limb may now come from other body structures. When this occurs the system is alerted that there is a conflict between motor and sensory systems and pain is experienced. Recently it has been shown that if this mismatch is corrected, using mirrors to provide the appropriate sensory response, then pain can be relieved in amputees and those with early complex regional pain syndrome (Ramachandran and Hirstein, 1998; McCabe et al., 2003b).

This pain mechanism theory is still in its infancy but its suggestion that pain can be experienced in the absence of pathology challenges the traditional view of a solely peripheral, nociceptive mechanism. It also enables us to reassess those perplexing conditions where pain exists in the absence of objective clinical findings

which may previously have been dismissed by a physician as 'psychosomatic'. These are predominantly chronic pain conditions where the doctor's 'disbelief' may further compound the patient's distress.

### Chronic pain and its psychosomatic implications

It is important to recognize the difference between acute and chronic pain, as the latter is not simply a longer duration of the former. Melzack and Wall (1996: 15–33) state that chronic pain is the result of 'multiple, interacting causes', which commonly do not respond to treatments used successfully in acute pain. This inability to cure chronic pain may result in behaviour changes in the sufferer who may describe a sense of helplessness or hopelessness. Keefe et al. (1980) describe the behavioural changes that may occur in the first two years of chronic pain and how the initial hope for a cure gradually progresses to disillusionment and possible depression. This disillusionment sometimes results in 'doctor shopping' where the patient moves from one doctor to another in the hope that a cure can be found. Fear, anxiety, depression and a sense of failure may ensue (Wall, 1999b). These changes may lead to patients constantly scanning their symptoms, focusing more attention on the pain, which only confirms that their condition remains unchanged or even perceived to be deteriorating. Catastrophizing can be the natural consequence of this over-attentiveness so that minor changes become a noteworthy event although, for some, this may also act as a coping strategy (Keefe et al., 1989).

Living with pain for a prolonged period can have a marked effect upon individuals and their quality of life: affecting relationships, employment, social activities and mood. These in turn can be influenced by gender, cultural beliefs, age and genetic factors. The confines of this paper do not allow for a more comprehensive review of these areas but this should not detract from their importance. Both physical and psychological factors interact with and contribute to chronic pain. The relationship and balance between the two should always be considered when assessing and treating a patient in pain.

### Rheumatology pain

We have seen that the experience of pain derives from both peripheral and central mechanisms (at the spinal and cortical level) which may be greatly influenced by an individual's current and previous life experiences. Each mechanism, or external influence may require a subtly different therapeutic approach to relieve that pain and ideally the clinician would be able to identify the primary mechanism involved and target therapies appropriately. The three brief case histories below describe the signs and symptoms that a patient with RA, OA or FMS may present with and

illustrate how, in practice, trying to identify one single cause is a futile exercise. The confines of this paper do not enable a more detailed analysis of each case history and the effect of specific, mechanism-targeted therapies on the symptoms of each individual. Rather, they demonstrate the complexity of the pain that patients may describe and the possible mechanisms that the clinician may wish to consider.

It must be stressed that our knowledge of pain mechanisms is far from complete and that much still relies on hypothetical conjecture.

### Case history 1: Rheumatoid arthritis

Patient A, a 42-year-old woman, was diagnosed with sero-positive rheumatoid arthritis three years ago. She works as a teacher at the local primary school and lives with her husband and two teenage children in a two-storey house. Until two months ago her disease was well controlled on 10mg of methotrexate once a week. In addition she takes a non-steroidal anti-inflammatory drug once a day and occasional paracetamol to ease pain and stiffness. She requests an early referral to her local rheumatology department as she is now experiencing a 'flare' of her disease that coincided with the start of the autumn school term. Her workload has increased due to staff sickness and she is concerned about the impact this is having on her children at home.

She describes prolonged early morning stiffness, pain and swelling over her metacarpal phalangeal joints, wrists, knees and metatarsal joints. Her pain is predominantly burning in quality and she is tender to touch. She also reports generalized tenderness in her upper arms and legs. She finds it difficult to climb the stairs at home and is kept awake by pain at night.

#### Possible pain pathways

##### Peripheral mechanisms

The inflammatory process, as demonstrated by redness, swelling and local tenderness over the joints, will have generated peripheral sensitization (primary hyperalgesia). Her report of burning pain suggests that this has involved her C-fibres or changes in the dorsal horn have resulted in central sensitization. Her pain on walking up stairs may be due to changes in the intra-articular pressure within her knee joints as an effusion may influence the mechanosensitivity of joint afferents so that on movement, articular pressure is increased in a diseased joint (Schaible and Grubb, 1993).

##### Central mechanisms

The report of generalized tenderness indicates a lowering of the A $\beta$ -fibre threshold which is characteristic of central sensitization (secondary hyperalgesia) and may have been induced by the duration of her symptoms. Changes in proprioception due



to joint damage and/or swelling of the joints may create a mismatch in motor and sensory systems and this mechanism has been proposed as one explanation for the perception of stiffness in rheumatoid arthritis (Haigh et al., 2003). Stiffness, as a distinct symptom separate from pain, has historically proved difficult to define. Three possible definitions were tested and discussed during the generation of the current American Rheumatism Association diagnostic criteria for rheumatoid arthritis (Arnett et al., 1988) and all had relatively low specificity (Edworthy, 1999). However, a more recent, patient-derived definition proposes that stiffness is a bilateral slowness or difficulty in moving the joints first thing in the morning or after prolonged sitting, which eases with movement (Lineker et al., 1999). Patient A's specific report of stiffness on rising would appear to meet this definition. Other factors that may be influencing Patient A's experience of pain and her ability to cope with it include: lack of sleep, and anxiety regarding her workload and family life.

## Case history 2: Osteoarthritis

Patient B is a 75-year-old man with a five year history of pain in his left knee and radiographic changes suggestive of osteoarthritis. He lives alone and is finding it increasingly difficult to walk to the shops and manage around the home. He was a keen golfer but due to his reduced mobility has found that this is no longer possible. He describes intermittent sharp, stabbing pains in his left knee, occasional swelling associated with burning pain and is concerned that his right knee is also starting to become painful.

### Possible pain pathways

#### Peripheral mechanisms

Under normal circumstances nociceptors in the immediate vicinity of the intra-articular cavity do not induce pain when stimulated by mechanical pressure (Kellgren and Samuel, 1950). This explains why some patients with OA report little pain despite severe radiographic changes (Kidd, 2003). However, these nociceptors can become sensitized in the presence of inflammation leading to peripheral sensitization as previously described. The sharp pain that Patient B reports may be attributable to the lowering of A $\delta$ -fibre threshold so that previously benign mechanical stimuli become painful. In addition, bone is richly innervated with sensory fibres and if oedema is present this too may be a source of his pain (Kidd, 2003).

#### Central mechanisms

The persistent peripheral sensitization may result in central sensitization so that Patient B feels pain and tenderness extending beyond the area of his knee.

Proprioceptive changes are inevitable due to the structural changes within the joint and the compensatory mode of walking Patient B will have developed. Sharma et al. (1997) and Pai et al. (1997) have both shown that patients with unilateral knee OA have worse proprioception in their affected and unaffected joints than elderly controls. This continuous sensory imbalance in the contralateral knee increases the risk of injury and ultimately of generating OA (Hurley, 1997) and this may explain Patient B's increasing concerns regarding his right knee. His increasing social isolation and distress at his reduced independence will both influence his pain experience.

### Case history 3: Fibromyalgia (FMS)

Patient C, a 36-year-old woman has recently been diagnosed with FMS. She is divorced and lives alone but does have her elderly parents living nearby. She resigned from a clerical job on the grounds of ill health as she felt 'too exhausted' to work and State benefits are now her only source of income. She reports widespread pain and sensitivity although she is specifically tender over the characteristic FMS trigger points. She also reports that her hands and feet frequently feel swollen although when she looks at them they do not appear so. Her sleep is poor despite low dose amitriptyline and she complains of 'an intense weariness' which is present all day. Her activity levels have reduced sharply and she relies on her parents to do all her shopping.

#### Possible pain pathways

##### Peripheral mechanisms

Despite Patient C's perception of swelling there is no inflammatory component to her disease and this is more likely to be a central mechanism manifestation. Pain on deep palpation over the trigger points is also likely to be attributable to central rather than peripheral sensitization as is the presence of her generalized sensitivity (Staud et al., 2001).

##### Central mechanisms

Patient C's symptoms are highly suggestive of centrally generated pain although with the cause of FMS still unknown, this can only be conjecture. Recent research increasingly suggests that neuroendocrine abnormalities may play a part in the generation of FMS pain. Her poor sleep and low exercise levels will reduce her natural production of endorphins and changes in the activity of serotonin and noradrenalin may further compound this (Neeck and Crofford, 2000). Her altered body perception may result in her actual sensory input no longer matching the

efferece copy so that pain and other sensory disturbances are generated. These sensations may be exacerbated by her general anxiety concerning financial pressures, reduced social contact, limited mobility and health of her ageing parents who are her only support system.

## Conclusion

The above case histories demonstrate the complexity of pain and highlight the need for a comprehensive patient assessment that may necessitate multi-dimensional therapy. Patrick Wall stated: 'It is inherently ridiculous to consider pain as an isolated entity although many do exactly that. Our understanding brains steadily combine all available information from the outside world and from within our bodies ... our personal ... and our genetic histories' (Wall, 1999b). Pain in the rheumatic diseases is no exception.

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Main articles

# **Appendix 2**

## Joint stiffness in a phantom limb: evidence of central nervous system involvement in rheumatoid arthritis

R. C. Haigh, C. S. McCabe, P. W. Halligan and D. R. Blake<sup>1</sup>

**Objective.** The nature and cause of perceived joint stiffness (PJS), a well-established and defining symptom of rheumatoid arthritis (RA), remains unclear. We hypothesized that changes in the central nervous system (CNS) may determine and maintain this subjective experience of stiffness in a limb even after it is amputated. To test this hypothesis, patients with a phantom limb (PL) who had experienced characteristic RA stiffness prior to amputation were systematically investigated.

**Methods.** Three patients with a current diagnosis of RA and lower limb amputation were investigated to determine the nature and pattern of pain and stiffness in their PL and intact limb. In addition to standard physical examination, pain and stiffness severity was measured using visual analogue scales for both limbs. The duration and timing of stiffness were also recorded for each limb.

**Results.** In all three cases, the pattern of perceived RA stiffness was similar for the intact limb and the PL. All three patients described stiffness in their PL which mirrored that of physical RA joint symptoms in terms of quality, frequency, diurnal variation, location, distribution and response to medication [non-steroidal anti-inflammatory drug (NSAID), corticosteroid, opiate and disease-modifying anti-rheumatic drug (DMARD)]. Unilateral exercise (or attempted exercise) relieved stiffness only in the limb being exercised.

**Conclusion.** The extent to which the subjective experience of perceived stiffness could be dissociated from the assumed original peripheral source was strikingly illustrated in RA patients with phantom limbs. We suggest that the PJS characteristic of RA is generated and maintained by secondary plastic changes in the CNS, although causally related to the initial peripheral rheumatoid disease process.

The nature and cause of stiffness in rheumatoid arthritis (RA) remain unclear, although it is a cardinal diagnostic symptom [1] and is used as a clinical indicator of the extent of disease activity. Currently, two qualitatively different uses of the term are employed. Objective joint stiffness (OJS) is operationally defined as the measurable resistance to passive movement when the joint is put through a normal range of motion in the usual functional plane [2]. This objective or mechanical stiffness, however, is not equivalent to the subjective complaint of localized immobility, a perceived resistance to self-initiated

movement, reported by patients with active RA [3, 4]. Using a microprocessor-controlled arthrograph, it has been shown that measures of OJS do not relate to the subjective experience. Indeed, compared with non-arthritic controls, OJS was reduced in RA joints [5].

We suggest, therefore, that it is clinically useful and theoretically important to distinguish two different uses of the clinical term 'stiffness' in RA. We propose that the common clinical complaint of subjective rigidity and immobility be described as 'perceived joint stiffness' (PJS). Following the qualitative findings of Lineker *et al.*

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TABLE 1. Clinical details of patients with RA and amputation

Patient	Age (yr)	Disease duration (yr)	Reason for amputation	Amputation level	Time after amputation
A	79	23	RA vasculitis and ulceration	Left through-knee	3 yr
B	63	24	Peripheral vascular disease	Right above-knee	4 months
C	77	25	Delayed non-union ankle fracture	Right below-knee	2 yr

TABLE 2. Characteristics of stiffness in phantom limb

Patient	Phantom swelling	PJS		Response to medication			
		Early morning	Gel phenomenon	NSAID	New DMARD	Corticosteroid	Opioid
A		+		+			-
B	+	+	+	+		+	-
C	+	+	+	+	+		

+, presence of symptom or positive response to medication; -, negative response to medication.

[4], we take PJS to refer to the variable set of subjective sensations (i) that can be triggered by preparing to move a joint or initiating a limb movement, (ii) that is more commonly pronounced in the morning, and (iii) in which the subjective content is commonly associated with and often indistinguishable from pain or discomfort. Traditionally, PJS has been attributed to local ongoing changes in the periphery. However, recent neurophysiological studies have demonstrated that pain states can be associated with plastic changes within the brain [6, 7]. For example, cortical reorganization is detected following sensory deafferentation and repetitive selective limb use [8, 9]. We therefore hypothesized that the central nervous system (CNS) is capable of generating a feedback-dependent state which can result in pathological sensations, such as pain and stiffness, that are to some extent independent of the initial peripheral pathology [7, 10]. Clinical evidence to support this proposal might be found by investigating the clinical presentation of PJS in RA patients who have undergone limb amputation but nevertheless retain an experience of a phantom limb. Indeed, by decoupling direct physical sensory feedback, such cases provide a great opportunity to understand the CNS mechanisms that may generate the characteristic subjective symptoms of PJS.

## Patients and methods

Patients were sought who fulfilled diagnostic criteria for RA prior to undergoing limb amputation. A search was made of the local hospital's database (RNHRD, Bath) and regional Artificial Limb Centre (Southmead Hospital, Bristol). Three patients were identified, and local ethics committee approval was given to approach them. A detailed history was taken of their phantom limb phenomena and of previous and ongoing RA. Questions were specifically asked about PJS in both intact and phantom limb joints. The location and duration of stiffness, the diurnal patterns and the response to medication were all detailed. The severity of stiffness was assessed using a visual analogue scale (0-10 horizontal; 0=no stiffness and 10=worst ever). We attempted to distinguish between a somatosensory memory and the phenomenological experience

of the current phantom limb. To do this, we asked patients to exercise their lower limb joints individually: voluntary but regulated physical movements of the intact limb, and voluntary but regulated imagined movements of the phantom limb. The time taken to ease stiffness and the change in severity of stiffness (if any) in each joint during exercise was noted.

## Results

The clinical details of the three subjects are presented in Table 1. All patients experienced a post-amputation phantom limb, a sensation of the missing limb and phantom limb pain, which is common and well described [11]. Moreover, all three patients claimed that they could voluntarily move their phantom limb. However, all subjects complained or reported, during investigation, a discernible sensation of stiffness (PJS) and inability to move the phantom limb joints freely. This was similar to that experienced in their limb prior to amputation and occurred at the same time as the stiffness in the remaining intact limb. This 'phantom stiffness' mirrored traditional RA joint stiffness symptoms in many, but not all aspects, as summarized in Table 2. In terms of the quality of the stiffness, all patients reported the same physical sensation of inability to move the joints freely in both the intact limb and the phantom limb. This feeling of stiffness was identical and carried with it the same distressing quality. The duration of stiffness in each limb was also similar. The phantom ankle and knee in patients B and C felt swollen in exactly the same manner as (though independent of) normal limb RA joints. When the intact limb joint flared, the phantom limb joint also flared (Fig. 1). The stiffness reported was similar in magnitude and faded concomitantly with the intact limb. Nocturnal and diurnal variation was also present. If stiffness woke the patient at night or the patient was awakened and noted that they were stiff, the stiffness was always present in both the intact and the phantom limb. The location and distribution of the stiffness followed the classic RA-like pattern in all patients. For example, in the foot, maximal stiffness was

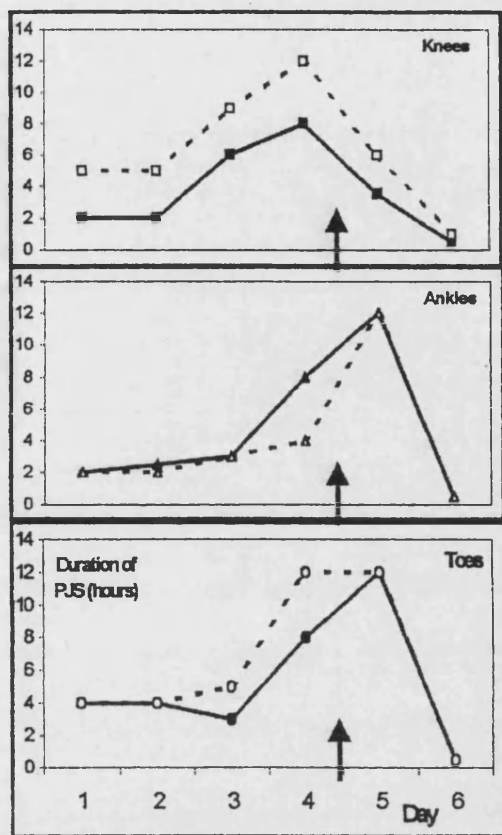


FIG. 1. Individual PJS in intact and phantom limb joints (knees, ankles and toes) and the influence of pulsed corticosteroid (patient B). Phantom limb PJS is represented by the interrupted lines and open symbols. Intact PJS is represented by continuous lines and filled symbols. Bold arrow indicates timing of corticosteroid pulse.

present in the toes located over the intact and phantom limb metatarsal joints. It was associated with a feeling of clawing of the toes, coupled with a desire to exercise. With post-rest stiffness, the usual 'gel' phenomenon occurred, and was similar in both intact and phantom limb. Phantom stiffness was also responsive to non-steroidal anti-inflammatory drugs (NSAIDs), mirroring the intact joints. Systemic administration of corticosteroid in patient B (Fig. 1) and a new disease-modifying anti-rheumatic drug (DMARD) in patient C improved both pain and stiffness in phantom limb and intact limb joints alike.

However, the stiffness reported in the phantom limb was not simply a mirrored duplicate of stiffness in the intact limb or a somatosensory memory of stiffness of the amputated limb. When asked to exercise (with eyes closed) the existing limb while keeping their phantom limb still, the intact limb joint rapidly lost its stiffness, as indicated by scores on the VAS, but had no effect on PJS of the phantom limb (Table 3). The converse was also true: 'exercising' the phantom limb had no effect on

TABLE 3. PJS severity and response to unilateral joint exercise (patient B)

	Toes		Ankle	
	VAS before exercise	VAS after exercise	VAS before exercise	VAS after exercise
Intact limb	7	4 (10)	7	4 (10)
Phantom limb	7	6 (35)	7	6 (60)

Figures in parentheses indicate duration of exercise (s) required to relieve PJS.

stiffness in the intact joint. Furthermore, in patient B the amount of exercise required to relieve stiffness in the phantom limb was at least three times that required to relieve stiffness in the intact limb. The reduction of stiffness for similar durations of exercise was slightly less in the phantom limb. For example, the severity of stiffness (0–10 visual analogue score) before and after exercise in the intact limb was 7/10 and 4/10 respectively, and in the phantom limb it was 7/10 (before) and 5.5/10 (after).

## Discussion

This report complements and extends previous studies of amputees, many of whom report significant levels of phantom pain. The presence and origins of arthritic symptoms in phantom limbs have not received clinical attention, nor have their implications for understanding the underlying mechanisms that generate the characteristic subjective symptoms of PJS. Consequently, there are no epidemiological studies of limb amputation in arthritis, nor are there any clinical reports describing the nature of phantom limb pain in RA patients. As PJS in these cases could not have been derived from the original peripheral pathology and the effect of limb exercise (phantom and intact limb respectively) was specific to the limb being exercised (ruling out pre-amputation memory), our findings indicate that the subjective experience of PJS is generated and maintained in the absence of continuous peripheral input from the amputated limb. If peripheral systems are not ultimately involved in generating and maintaining the subjective experience of PJS, which brain systems are involved?

Our findings are consistent with recent clinical observations and neurophysiological findings which show that neuroplastic changes in the brain are sufficient to explain some chronic pain conditions. Harris [10] proposed that many pains may have cortical origins. We suggest that PJS (a qualitatively distinct form of discomfort) could also have its origins in brain mechanisms responsible for monitoring the consequences of motor intention and, in particular, the expected or predicted sensory feedback generated at the time planned movements are initiated. These feed-forward and inverse models have been extensively reviewed by Wolpert [12]. In summary, each time a motor command is issued, an

effluent copy of that motor command is produced in parallel. This provides the basis for predicting the consequences of the actual movement. In most cases, the normal awareness and experience of our limb is based on the predicted state rather than the actual state [13]. If the system monitoring feedback detects a deviation from the predicted state, a subjective experience of over- or undershoot is reported, as in the case of pointing or grasping [13]. Even in the absence of feedback from a physical limb (i.e. a phantom limb), motor commands from frontal brain areas can still be issued which produce a predicted state whereby the phantom is experienced as moving.

In RA, we suggest that dysfunctional proprioceptive information processing produces impaired efferent copies that are largely responsible for these patients' experience of stiffness and indeed pain. Over time, this distorted information is used to predict the expected sensory and conscious correlates of a limb movement. Production of an impaired efferent copy will consequently activate brain areas that monitor the conflict between motor intention and appropriate sensory feedback [10, 14]. This qualitatively altered perception is experienced and reported as stiffness rather than stabbing or shooting pain because it is triggered by preparing to move a joint or initiate a limb movement and not the movement *per se*.

Our observation that the movement of a phantom limb fails to relieve stiffness to the same extent as movement of the intact limb highlights the importance of actual (albeit impaired) peripheral feedback in modulating stiffness symptoms. Furthermore, the lack of effect of unilateral exercise on the opposite knee joint rules out a pain-mirroring mechanism from the contralateral joint. A period of short but continuous exercise allows updating of the impaired efferent signals, albeit only temporarily. Moreover, joint exercise accompanied by visualization of the moving limb—as patients do with their hands when describing stiffness in the clinic—may further enhance the modification of the efferent copy with input from another modality. Similarly, sensory interventions, such as hydrotherapy, hand immersion in hot wax and taking a shower in the morning, could provide the additional cutaneous sensory feedback required to correct inaccurate predictions of the existing efferent copy.

We consider it unlikely that the phantom RA represents a 'somatosensory memory'. As a clinical presentation, the condition is clearly described by the patient as an experience rather than a semantic memory. This qualitative distinction by the patient also finds support in several recent functional imaging studies of phantom limb patients and referred sensations, in which experience and reported movements of the phantom limb are associated with selective activations in sensory-motor brain areas normally involved in limb movements [15–17].

The final common pathway for the generation of PJS is the conflict between the predicted (efferent copy) and actual states, caused by inaccurate sensory information.

Are there conditions in RA that create these conflicts of motor and sensory information? Such incongruence may be signalled via a number of routes, and both neural mechanisms and centrally acting circulating mediators may be involved. Firstly, inappropriate cortical representations, as a consequence of impaired proprioceptive input, can generate conflict between the senses [10]. Functional imaging studies provide evidence of cortical changes at several levels in RA [18–21]. Secondly, neural mechanisms include distorted position sense [22], impaired sensory feedback from partially denervated joints [23] and the functional consequences of peripheral and CNS sensitization. Thirdly, circulating factors include inflammatory mediators and cytokines, such as tumour necrosis factor  $\alpha$  and interleukins, which may trigger CNS centres and enhance peripheral nociceptor responses. Cytokines can recruit central stress-responsive neurotransmitter systems involved in the modulation of the immune response and in the activation of behaviours that may be adaptive during injury or inflammation [24–26]. Previous work has shown that variation in levels of these mediators, coupled to activity of the hypothalamic–pituitary–adrenal axis, may be related to the circadian pattern of stiffness [27, 28].

In conclusion, we report three patients with RA stiffness in their phantom limb. The characteristics of this PJS were very similar in some aspects, whilst crucially different in others, to that of PJS in the diseased remaining limb. On this basis, we argue that the experience of peripherally located stiffness results from impairment of central brain processes. In reformulating the accounts of both Ramachandran *et al.* [8] and Frith *et al.* [13] for phantom limb experience, we suggest that dysfunctional sensory processing in RA produces impaired efferent copies of the planned motor commands and expected sensory consequences. This is ultimately perceived as stiffness by the patient with RA.

### Acknowledgements

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# **Appendix 3**

Study number .....

**Participant Consent form**

**A single centre pilot study to investigate whether referred sensations exist in Complex Regional Pain Syndrome (CRPS) and the effect of mirror visual feedback on CRPS pain.**

Sister Candy McCabe, ARC Lecturer in Rheumatological Nursing  
Professor D. Blake, Professor of Bone and Joint Medicine

Please initial box

1. I confirm that I have read and understand the information sheet for the above study. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without my medical care or legal rights affected. ☐
3. I am willing to allow access to my medical records but understand that strict confidentiality will be maintained. ☐
4. I agree to take part in the above study ☐

\_\_\_\_\_  
Name of participant

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Name of person taking consent  
(if different from researcher)

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Researcher

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature

# **Appendix 4**

Study number .....

**Participant Consent form**

**A research study to assess if proprioceptive abnormalities in the rheumatic diseases can be identified with mirror visual feedback**

Professor D. Blake, Professor of Bone and Joint Medicine  
Dr. R. Haigh, arc Clinical research Fellow  
Sister Candy McCabe, arc Lecturer in Rheumatology Nursing

Please initial box

1. I confirm that I have read and understand the information sheet for the above study. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without my medical care or legal rights affected. ☐
3. I am willing to allow access to my medical records but understand that strict confidentiality will be maintained. ☐
4. I agree to take part in the above study. ☐

\_\_\_\_\_  
Name of participant

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Name of person taking consent  
(if different from researcher)

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Researcher

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature

# **Appendix 5**

## **Participant Information Sheet**

**A research study to assess whether referred sensations exist in Complex Regional pain Syndrome (CRPS) and the effect of mirror visual feedback on CRPS pain.**

You are being invited to take part in a research project. Here is some information about the project to help you decide whether or not to take part. Please take time to read the following information carefully and, if you wish, discuss it with your family, friends and your GP. Take time to decide whether or not you wish to take part.

### **What is this research project all about?**

In rheumatology we have long been aware that our patients sometimes describe to us certain types of pain which we cannot give a physical explanation for. Research work in other areas, such as that on amputees with phantom limb pain, has shown that pain can occur when there is an imbalance between what your body intends to do and what it feels it is doing. When this imbalance is present some people may experience pain. Some researchers have used mirrors to try to correct this imbalance and change the levels of pain. We are interested to see if patients with Complex Regional Pain Syndrome (CRPS) suffer from this particular type of pain. We are also interested to see which areas of the body are sensitive to touch in CRPS as this may help us to better understand the cause of CRPS pain.

### **What would I be asked to do?**

We are inviting you to undergo some assessments on two occasions which we will include in your routine clinic appointments (or whilst you are a patient on the ward). The first set of assessments will be conducted when you are first seen by a member of Professor Blake's team, the second one six weeks later. All assessments will be conducted either on the ward, if you are inpatient, or in the outpatient department at the Royal National Hospital for Rheumatic Diseases.

The assessments will involve the following:

**Record of levels of pain and frequency of mirror use**

We will ask you to complete a brief assessment of your pain when you are seen at each visit and keep a daily record of this, and your use of the mirror, during the six week period in between visits.

**Assessment to see where you are sensitive to touch**

We will examine you with your eyes open and closed to see where you feel light touch, pinprick, temperature and vibration. We will examine all your limbs, face and lower spine. We may need to mark the site you feel the sensation with a pen and record it as a still photograph. If this is the case we will discuss this further with you at the time and ask you to sign a separate consent form.

**Mirror visual feedback**

We will help you to position a mirror (which has a whiteboard on the reverse) between your painful and non-painful limb and ask you to first look at the whiteboard and then the reflection of your non-painful limb, in the mirror. We will assess your pain levels at rest and when you perform some very simple exercises. At the end of the first assessment we will give you an information sheet telling you how to continue using the mirror during the time between visits. The information sheet tells you how often to use the mirror and which movements to perform as you look in to it.

**Are there any benefits or risks in taking part?**

We do not know yet whether you will find any benefits from this research. However, we are not aware of any risks but you may find it feels a little peculiar to see the mirror image of your non-painful limb where you feel your painful limb to be.

**Do I have to take part?**

No, taking part is quite voluntary and if you would prefer not to, nobody will be upset. If you do agree to take part you are free to withdraw from the study at any time without giving a reason and without it affecting the care you receive. If you do decide to participate in the study, your GP will be informed, unless you do not want your GP to know.

Thank you for considering taking part in our research. If you have any questions please do not hesitate to contact one of the researchers listed below.

Sister Candy McCabe 01225 465941 x208

Professor D. Blake & Dr. R. Haigh 01225 465941 bleep 42.

# **Appendix 6**



## **Participant Information Sheet**

### **A research study to assess whether a mirror can affect where you sense your joints are and how they move in space.**

You are being invited to take part in a research project. Here is some information about the project to help you decide whether or not to take part. Please take time to read the following information carefully and, if you wish, discuss it with your family, friends and your GP. Take time to decide whether or not you wish to take part.

#### **What is this research project all about?**

In rheumatology we have long been aware that our patients sometimes describe to us certain types of pain which we cannot give a physical explanation for. Research work in other areas, such as that on amputees with phantom limb pain, has shown that pain can occur when there is an imbalance between what your body intends to do and what it feels it is doing. When this imbalance is present people are not so aware of where their arms or legs are in space. We are interested to see if patients, with particular types of joint problems, are less aware of where their limbs are in space than people who do not have joint problems.

#### **What would I be asked to do?**

We are inviting you to attend the outpatient department on one occasion and perform some simple exercises that will take about one and a half hours. We will be using a mirror in two separate sets of exercises so that we can, for a short time, alter where you feel your arms and legs are in space. We will ask you some questions about how your arms and legs feel during and after each exercise. All the information we collect will be stored anonymously and be completely confidential.

#### **Are there any benefits or risks in taking part?**

There are no particular benefits to you personally. You may find that during some of the exercises you feel some strange sensations in your arms or legs. These should not be painful but may be a little uncomfortable and if at any time you wish to stop the assessment, you are free to do so. These sensations should last for no more than a few minutes and will certainly be gone in half an hour.

**Do I have to take part?**

No, taking part is quite voluntary and if you would prefer not to, nobody will be upset. If you do agree to take part you are free to withdraw from the study at any time without giving a reason and without it affecting the care you receive.

Thank you for considering taking part in our research. If you have any questions please do not hesitate to contact one of the researchers listed below.

Sister Candy McCabe 01225 465941 x208

Professor D. Blake & Dr. R. Haigh 01225 465941

# **Appendix 7**

Name.....	Hospital ID.....
Address	D.O.B
Please affix patient ID label here.	
GP	

Dear Dr .....

This is to inform you that the above patient has agreed to participate in a research study looking at whether referred sensations are present in Complex Regional Pain Syndrome (CRPS) and the effect of mirror visual feedback on CRPS pain.

CRPS is a painful, debilitating condition which is frequently resistant to a wide range of treatments. Recent studies on other intractable pain conditions, particularly Phantom Limb Pain (PLP), have reported the analgesic benefits of mirror visual feedback therapy. PLP has many similar characteristics to CRPS pain (burning, cramping and mislocalisation and referred sensations have been widely reported in amputees providing evidence of central sensory reorganisation. Sensory and motor disturbances are known to occur in patients with CRPS and our patients routinely report an altered body image. We wish to establish if referred sensations are present in this population, indicating cortical sensory plasticity, and whether mirror therapy will correct the resulting mismatch between motor intention and sensory input.

Each patient will be seen on presentation and six weeks later at the RNHRD. In addition to the routine clinical assessments which include thermal imaging and neurological testing the following will be performed: recording of levels of pain and frequency of mirror use in a daily patient record. Each patient will have their pain levels assessed, using visual analogue scales, whilst they view the control device (a whiteboard) and the intervention (a mirror). Pain at rest and on movement will be recorded. Individual guidance will be given to each subject for the period between assessments. This will outline the duration of mirror usage and the type of movements to be performed whilst viewing the mirror.

If at any time your patient consults you about symptoms or problems possibly related to the study, please refer them to Professor D. Blake as soon as possible.

If you would like further information or have any queries, please contact:

Sister Candy McCabe Tel. 01225 465941 x 208,  
Prof. David Blake Tel. 01225 465941 x 441

Thank you for your co-operation.

SIGNED..... (Name and position).....  
DATE:.....

# **Appendix 8**

# Referred sensations in patients with complex regional pain syndrome type 1

C. S. McCabe, R. C. Haigh, P. W. Halligan<sup>1</sup> and D. R. Blake

**Objectives.** This study sought to explore and characterize referred sensations (RS) in patients with complex regional pain syndrome (CRPS) type 1 and test the hypothesis that pain in CRPS is associated with central sensory changes.

**Methods.** Subjects underwent standardized neurological examination involving light touch, pinprick and vibration sense with eyes closed and then with eyes open. The subjects described the location and sensation emanating from the stimulated site and whether they experienced any sensations (similar or different) elsewhere.

**Results.** Five of 16 subjects recruited demonstrated RS. These were experienced in real time, were modality specific (touch and pinprick) and were located on the body part immediately adjacent, on Penfield's cortical homunculus, to the stimulated site. The RS were diminished or absent when the subject visualized the stimulated area. They disappeared when stimulation ceased and on clinical improvement.

**Conclusions.** This is the first report of RS in CRPS and provides further evidence of central reorganization in what was previously thought to be a peripheral disorder.

**KEY WORDS:** Complex regional pain syndrome type 1, Referred sensations, Central reorganization.

Referred sensations (RS) are somatosensory feelings that are perceived to emanate from a body part other than, but in association with, the body part being stimulated. They have been reported following limb amputation [1], somatosensory deafferentation [2], local anaesthesia [3], stroke [4] and spinal cord injury [5]. Collectively these studies have shown that the referred sites (the body part not physically touched) are non-random and often closely correspond to the body structure that is immediately adjacent to the stimulated site on the cortical topographical map first described by Penfield [6]. In the case of an amputated upper limb, patients report sensation in their phantom when parts of the face are lightly stroked [1]. These aberrant somatosensory, but reliable, sensations were interpreted as resulting from central sensory reorganization following disconnection or dysfunction of sensory pathways [1].

Sensory and motor disturbances occur in patients with complex regional pain syndrome (CRPS) [7]. This condition usually follows after a minor peripheral injury to a limb, but may occur spontaneously. It may be acute or chronic; type 1 is differentiated from type 2 by the

absence of neural trauma [8]. The clinical features of CRPS are well described and can be divided into five main areas: pain, oedema, autonomic dysfunction, movement disorder and trophic changes [9]. Pain is the dominant feature with patients typically describing a burning sensation that occurs spontaneously or spreading beyond the site of injury. The pain may be intermittent or persistent and specific sensory changes may include, allodynia, hyperalgesia and hyperaesthesia. Hemisensory impairment with decreased temperature and pinprick sensation ipsilateral to the CRPS-affected limb has also been reported [10]. This may involve the CRPS-affected limb only or encompass a more extensive area on the same side of the body. Where the latter, more generalized sensory deficit occurs this has been shown to correlate significantly with longer disease duration and a higher report of mechanical allodynia/hyperalgesia [11]. It has been proposed that these changes are attributable to functional disturbances in the processing of noxious events in the thalamus and a hemisensory deficit is indicative of subcortical brain plasticity. What has not been described previously is the presence of sensation in

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another body part when the painful site, or an area distal to that site, is stimulated, i.e. referred sensations (RS).

CRPS pain shares many similar characteristics to amputee phantom limb pain, mislocalized, intense and burning. As neural plasticity occurs in a variety of pain syndromes [12, 13] and because of the nature of CRPS pain, we predicted that if the disturbed peripheral sensations in CRPS type 1 were associated with central sensory changes, then evidence of this would be found in some patients as referred sensations. Furthermore, we hypothesized that these referred sensations would be perceived to emanate from the body structures immediately adjacent to the stimulated site and in keeping with their topographical location on the Penfield homunculus as in phantom and allied pain states. We specifically selected those patients with CRPS type 1 as we wished to discover whether central reorganization occurs even where there is no evidence of local peripheral nerve damage.

We therefore set out to explore and characterize referred sensations in patients with CRPS type 1 and we present five case studies where referred sensations were found to be present. The Bath Local Research Ethics Committee granted ethical approval and informed patient consent was gained.

## Method and participants

### Participants

Subjects who conformed to the diagnostic criteria for CRPS type 1 [14] were recruited over a 2-yr period from the out-patient and in-patient departments of the Royal National Hospital for Rheumatic Diseases, Bath.

### Methods

Subjects were assessed on initial presentation and weekly until either symptom resolution occurred or, in those with chronic

disease, discharge from in-patient care. Each assessment took the following format.

Subjects were placed in a supine position with the head of the couch elevated so that they could view all their limbs. They were asked to close their eyes and describe to the researcher any sensations they were experiencing, first in their unaffected limbs and then their affected limb. This first stage was used to accustom the subjects to focusing upon themselves and to establish baseline descriptions for unaffected limbs. Where the upper limb was affected the subject was first questioned about their legs followed by their unaffected upper limb and finally the affected limb. Conversely when the lower limb was involved the upper limbs were described first.

All subjects then underwent a standardized neurological examination testing light touch, pinprick and vibration sense first with their eyes closed and then with their eyes open. All limbs, lower spine and face were examined and sham trials, combined with a random order, were employed to reduce the possibility of patient suggestibility. Each time the subject was touched they were asked to describe the location of the stimulated site, the sensation emanating from it and whether they experienced any sensations (similar or different) anywhere else.

## Results

Over the 2-yr recruitment period, 16 subjects (13 female and three male) who met the entry criteria were recruited. Only five showed evidence of referred sensations and it is the findings of these five (four female and one male) that will be presented (Table 1). There was no difference in age, disease duration, levels of pain or severity of disease (Table 2) between those who presented with RS and those who did not.

The five subjects had a disease duration of 3 weeks to 6 yr (median 3 yr) and were aged from 24 to 57 yr (mean 36.8 yr). All had a single limb affected (two upper limb, three lower limb). In four cases (cases 1, 3, 4 and 5) the condition was spontaneous in onset and only in case 2

TABLE 1. Details of the five patients who showed evidence of referred sensations

Patient	Pain site	Disease duration	Area touched (1) Referral site (2, 3)	Direction of referral	Type of sensation	Loss of referred sensation	Resolution of CRPS (weeks)
Case 1 28 yr F (Fig. 1a)	Left hand	3 weeks	L 3rd fingertip (1) L lower jaw (2)	1-2	Light touch and pinprick	3 weeks	6
Case 2 34 yr F (Fig. 1b)	Left ankle	8 weeks	L forefoot (1) L patella (2)	1-2 and 2-1	Light touch and pinprick	3 weeks	4
Case 3 24 yr M (Fig. 1c)	Left knee	3 yr	L patella (1) L forefoot (2)	1-2 and 2-1	Light touch	No change	Chronic
Case 4 41 yr F (Fig. 1d)	Right foot	6 yr	R forefoot (1) R patella (2)	2-1	Light touch	4 weeks	Chronic
Case 5 57 yr F (Fig. 1e)	Left hand	4 yr	L shoulder (1) L ear (2) L hand (3)	1-2 1-3	Pulling, light touch and hand movement	No change	Chronic
(Fig. 1f)			L cheek (1) L hand (2)	1-2	Light touch		

TABLE 2. Details of all 16 patients

Case	Age (yr)	Gender	Disease duration	Affected limb	Pain level on movement at presentation <sup>a</sup>
1 <sup>b</sup>	28	F	3 weeks	Left hand	8
2 <sup>b</sup>	34	F	8 weeks	Left ankle	8
3 <sup>b</sup>	24	M	3 yr	Left knee	8
4 <sup>b</sup>	41	F	6 yr	Right foot	9
5 <sup>b</sup>	57	F	4 yr	Left hand	5
Mean <sup>b</sup>	36.8	4F:1M	2.6 yr		7.6
6	38	F	6 weeks	Left ankle	9
7	35	F	5 months	Right arm	5
8	40	F	1 yr	Right arm	6
9	38	F	3 yr	Left leg	5
10	27	M	2 yr	Left leg	8
11	51	F	2 yr	Right arm	7.5
12	68	F	1 yr	Left arm	5
13	54	M	4 yr	Left foot	9
14	38	F	7 yr	Left foot	10
15	22	F	4 yr	Left foot	9
16	59	F	10 yr	Left foot	9.5
Mean	42.7	9F:2M	3.1 yr		8

<sup>a</sup>Visual analogue 10-cm scale.<sup>b</sup>Referred sensations reported.

did it occur following injury. All reported pain that extended beyond the originating site with associated allodynia, hyperalgesia and vasomotor changes. None of the subjects had ever reported any previous perception of referred sensations to their physician.

#### Case 1

A 28-yr-old woman was admitted for in-patient rehabilitation with a 3-week history of progressive pain in her left hand for which there was no obvious triggering event. Her initial symptoms, prior to the onset of pain, were that of mottling of the fingertips. An intense burning pain involving all four fingers, but excluding the thumb, rapidly followed. Cold and light touch aggravated the pain and feeling of swelling. The patient held her limb in a flexed and pronated position close to her chest. Her hand was cold to touch and quantitative thermal imaging identified a 2.0°C temperature difference between the right and left forearms with the left cooler.

With her eyes closed she described her hand as excessively large 'like a blow up hand'. This phantom sensation of swelling extended to the thumb, despite no perceived involvement of this digit in her pain description. The patient was aware that this sensation was disproportionate to the degree of swelling that she observed. When the tip of the third finger of the affected hand was touched with a cotton bud, still with eyes closed, she experienced a stroking sensation over the lower left jaw (Fig. 1a). This sensation was modality specific with the subject reporting a pinprick sensation on her lower left jaw when the same finger was touched with a needle. The referred sensation only occurred at the time that the third finger was touched and there was no residual effect once the researcher stopped. Vibration was not referred. When the subject's left lower jaw was touched there were no reciprocal referred sensations experienced in the left hand.

The above examination was repeated with the subject looking at their hand as their affected limb was touched. Permitting direct visual feedback prevented the experience of referred sensations.

Over the next 2 weeks the referred sensations could be evoked at each assessment. However, by week 3 the subject no longer perceived her hand as swollen and referred sensations were lost. By 6 weeks all vasomotor changes were reversed and no pain was felt.

#### Case 2

A 34-yr-old woman presented to the out-patient department 8 weeks after an industrial accident, sustaining a minor injury to her left foot but no neural trauma. The initial pain of the injury settled, but returned 2 days later. On admission she described a stabbing pain from the toes to mid-calf. The foot was swollen, mottled in colour, hyperalgesic, allodynic and hyperhydrotic. The foot and calf were cold to the touch. Quantitative thermal imaging showed a 2.5°C difference between the right and left foot.

With her eyes closed the subject noted that her left foot appeared enlarged, greater in size than when she looked at it. During examination for referred sensations she reported that when her left knee was touched with a cotton bud, she felt a similar sensation on the plantar aspect of her left foot around the base of her metatarsophalangeal (MTP) joints (Fig. 1b). When this area on her left foot was touched, a similar sensation was experienced in her left knee. She had not sustained any injury to, or experienced any pain in, this knee at the time of her accident. The reality of these referred sensations was such that the patient was able to differentiate between light touch and pinprick sensory modalities at both referred sites. There were no referred sensations reported for the non-painful lower limb. Again, when the



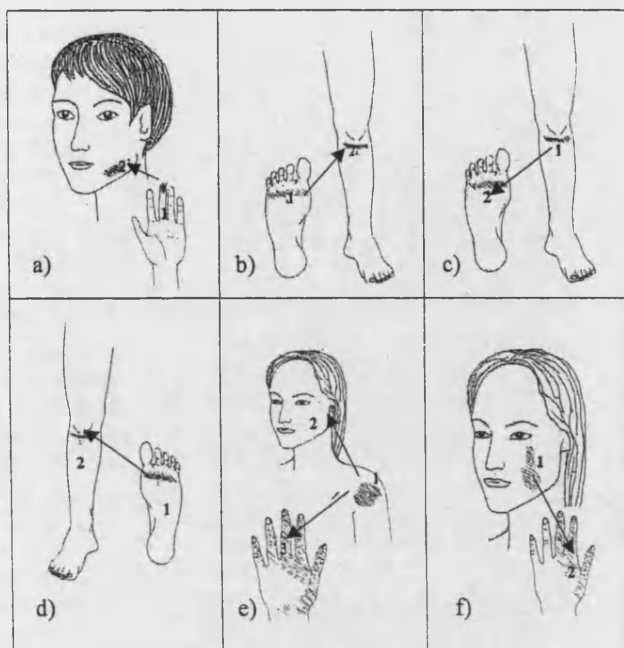


FIG. 1. Artist's impression of cases 1-5 illustrating location of stimulus and direction of referred sensation. (a) to (d) correspond to cases 1 to 4, (e) and (f) correspond to case 5. Shaded area (1) depicts area stimulated by examiner, shaded areas 2 and 3 depict where referred sensations were felt. The arrows illustrate direction of referral.

subject watched the examiner touch her affected limb, no referred sensations were reported.

This bidirectional referral of sensations could be evoked at the next two assessments but by week 3, following intensive physio- and hydrotherapy, the subject's pain and swelling had greatly improved and referred sensations were lost.

### Case 3

A 23-yr-old man was referred and admitted for rehabilitation. Three years previously he had woken with a spontaneously swollen left knee. No evidence of arthropathy was found despite full investigation including arthroscopy, synovial biopsy and MRI. He was aware of an extreme burning pain and the knee felt as if a 'red hot poker' was touching it. This pain persisted for 8 months and was unaffected by analgesics or steroid therapy. He had a nerve block which improved his symptoms for approximately 15 months. He then noticed colour changes in his left ankle and increasing tenderness. Two weeks later his knee became painful again. He underwent a wide number of different therapies (physiotherapy, TENS, acupuncture, nerve blocks), all of which had little or no effect upon his symptoms.

On admission he complained of intense burning pain in his left knee and ankle, was reluctant to move his leg and walked on crutches. Both his left ankle and left knee joints were moderately swollen and mottled in colour. He complained of hyperalgesia from toes to mid-calf. There was a  $1.7^{\circ}\text{C}$  difference between his left and right

leg with the left cooler. His right leg was completely normal in colour and sensations.

With his eyes closed he perceived that his left knee was twice the size of his right, his left ankle slightly enlarged and his toes larger than the rest of his left foot. When he was touched with a cotton bud below his left patella, he complained of feeling the same sensation on the plantar aspect of his left foot in the region of his MTP joints (Fig. 1c). A similar sensation was felt again in his left knee when the same region of his foot was touched. He was unable to differentiate between light touch and pinprick; both evoked the same feeling of 'discomfort'. The sensations were not present when the subject viewed the examiner touching his limb or when vibration was used.

Throughout this subject's 3-week in-patient stay, the referred sensations could be elicited. Although his mobility had marginally improved on discharge, his pain continued at the same level and his left knee remained swollen.

### Case 4

A 41-yr-old woman was referred to the out-patient department with a 7-yr history of pain in her right foot following a Wilson's osteotomy. She had had delayed healing post-surgery which had required an extended period of immobilization and, despite tricyclic antidepressant therapy and multiple episodes of physiotherapy, she had experienced persistent pain, primarily around her right MTP joints, ever since. On presentation she described a throbbing pain which extended beyond the site of initial injury and was exacerbated by weight bearing. She had allodynia, hyperalgesia in her right foot and dysaesthesia on the lower third of her right shin. There was swelling around her MTP joints and a temperature difference of  $0.8^{\circ}\text{C}$  between her right and left lower legs with her right cooler.

With her eyes closed she perceived her right knee and ankle to feel 'heavier' than her left and her right foot to be twice the size of her left. When she was touched with a cotton bud on the sole of her right foot, under her MTP joints, she reported feeling the same sensation in her right calf. When light touch was applied to the anterior of her right knee, in the patellar tendon area, this was referred distally to the dorsum of her right foot (Fig. 1d). The same sensations were evoked with a neurotip but not perceived as sharp in the referral site. Vibration was not referred and all referred sensations were lost when she viewed the area being touched.

Over the next 6 months this woman received a novel treatment of mirror visual feedback [15] and was reviewed monthly. Her pain reduced from 6/10 at rest to 1.7/10 as measured by a visual analogue scale and the perceived excessive swelling of her right foot diminished. The referred sensations found on presentation could not be re-evoked at any of her follow-up appointments.

### Case 5

A 57-yr-old woman was referred with a 4-yr history of CRPS affecting her left hand and was admitted for

rehabilitation. The condition had occurred spontaneously and persisted despite nerve blocks, physiotherapy, acupuncture and Gabapentin. She had fixed flexion deformities of the fingers on her left hand with an extended index finger and complained of intermittent dystonia. Her hand was swollen with allodynia and hyperalgesia present from her fingertips to elbow. Thermal imaging showed a 1.6°C difference between the right and left forearms with the left cooler.

With her eyes closed she described her left hand, from her fingertips to wrist, as feeling tight and larger than the right. When a cotton bud touched her left upper arm she felt a pulling on her left ear (Fig. 1e). This sensation was felt again when she was touched on the left shoulder but, in addition, she now reported that she felt her left thumb, fingers and wrist were also being touched. The referred sensation in her hand increased her pain at rest, from 5/10 to 8/10 on a verbal 10-point scale and her fingers involuntarily became more clawed. When the cotton bud was moved away from her shoulder the sensations in both her ear and hand disappeared, the pain gradually diminished and her fingers relaxed. The referred sensations in the left thumb, fingers and wrist were re-evoked when the left cheek was touched (Fig. 1f). Pinprick evoked the same sensations as light touch at all of the above-mentioned referral sites, but was not perceived as sharp. Vibration was not referred. When the subject viewed her limbs and face being touched, with the aid of a mirror, she reported a tightening in her left fingers but this was to a lesser extent than when she had her eyes closed. Her hand did not become clawed and her pain levels remained at pre-examination levels. The referred sensation of pulling on her left ear and touch on her left hand were not present with vision.

This woman's condition remained unchanged throughout her 2-week in-patient stay and the referred sensations remained constant.

## Summary

All patients reported referred sensations during examination with their eyes closed. They were experienced in real time and disappeared when stimulation ceased or vision was permitted. When the subjects viewed the area being touched the sensations were either diminished (case 5) or not present and when the symptoms of CRPS resolved (cases 1, 2 and 4), referred sensations were lost. Sensations were referred in a modality-specific manner with touch referred in all cases and pinprick also referred in two (cases 1 and 2). Vibration was never referred. All referred sites were located on body parts immediately adjacent, on Penfield's homunculus, to the stimulated site.

## Discussion

This is the first report of referred sensations in CRPS. The novelty of this finding may be due to clinicians not expecting such anomalous sensations or failing to see the

potential significance when patients may have reported them. In addition, examining patients with their eyes closed is not routine clinical practice in rheumatology. Light touch was the main sensation referred and this fits well with reports of referred sensations in other conditions [4, 16]. When these sensations are present in amputees, touch is typically the modality referred, with vibration, pinprick, temperature and stroking sensations less so [1].

Light touch is perceived when Ab fibres (large myelinated) are stimulated, though in CRPS Ab fibre stimulation has been found to elicit the experience of pain [17]. However, vibration is also transmitted by Ab fibres, but referral of this modality was not found in our patient sample. Interestingly, Rommel *et al.* [11] showed an increase in the touch threshold on the ipsilateral side of the CRPS-affected limb using quantitative sensory testing. They concluded that as this deficit extended beyond the area affected by CRPS it was unlikely that systematic damage was occurring at the primary afferents and this was more likely to be due to changes in processing within the central nervous system. In our study we also found that only those with early CRPS (<8 weeks) felt pinprick referred sensations and this may relate to Rommel *et al.*'s finding that those with significantly longer disease duration had a higher incidence of generalized sensory deficits [11]. However, it is difficult to state conclusively the significance of this result in the light of the small sample size. Referral of temperature was not assessed in this study.

The locations of the referred sites, in our study population, are consistent with previous reports in other pain conditions [1, 18] and fit particularly well with predicted cortical changes that have been shown to occur within the somatosensory body map [19]. Ramachandran [16] proposed that owing to the location and speed with which referred sensations occur in amputees, such 'ectopic representations' following functional remapping were probably due to the unmasking of latent synapses within the cortex, as previously described in primates [20, 21]. These synapses are suppressed when there is simultaneous input from two connected receptors, but with reduced or impaired sensory activation in one area, the connection becomes disinhibited. Recent imaging studies, using magnetoencephalography, in six patients with upper limb CRPS type 1 have also shown changes in the cortical somatosensory map, though it was not reported whether these were associated with referred sensations [22]. There was a significantly shorter distance between the areas representing the thumb and little finger on the somatosensory cortex contralateral to the affected limb than the ipsilateral side. Interestingly, there was no significant correlation between the distance of thumb and finger and the level or duration of pain.

Alternatively, referral of sensations may occur at the spinal level. A large body of evidence shows that sensitization of wide dynamic range neurons at level V of the dorsal horn results in ipsilateral and contralateral enlarged receptive fields, which do not rely on a cortical homunculus [23]. In addition, experimental models of

peripheral neuropathic pain all demonstrate bilateral spinal cord changes after unilateral nerve damage [24]. However, all of our patients had CRPS type 1, so therefore had no precipitating neural trauma. Their sensations were not referred bilaterally, either from the stimulated site to its contralateral partner (i.e. left hand to right hand) or mirrored on the contralateral side (i.e. from stimulated site to referral site on the unaffected limb). In addition, the speed of referral in terms of disease duration, response time on stimulation and resolution as the condition improved, combined with the magnitude of the sensations, all detract from a purely spinal route. Recent thinking is that CRPS is a disorder that involves both CNS and peripheral nervous system components [25, 26]. This is based on the evidence that some patients respond positively to sympathetic blockade, thereby implicating involvement of the sympathetic nervous system, but conversely, sympathetically maintained pain involves the deep somatic tissue (as demonstrated by our patients report of increased pain on movement) which is the domain of the autonomic system. Therefore isolating one clear route for referred sensations is at present problematical.

The reason for the reduction of sensory input in amputees is clear, but in CRPS, where the affected limbs are hypersensitive, one may expect there to be greater sensory input. One explanation is that in CRPS we are seeing a pathological increase in sensory input from one area and hence encroachment of adjacent brain parts following the relocation of the limb's representation in the sensory map as suggested by the recent imaging studies [22]. Another proposed theory is that the excessive sensory input from the painful area of the affected limb results in a decreased perception of other sensory input from the remaining half of the body, resulting in a functional 'neglect syndrome' as demonstrated by a hemisensory deficit [10]. Conversely, it is possible that the considerable sensory dysfunction within the peripheral parts of the painful limb is registered as a loss and the adjacent areas, on Penfield's homunculus, now encroach. Whichever scenario occurs, the findings from our five case reports show that the processes underlying referred sensations are reversible over a short period of time. Moreover, these processes do not produce referred sensations in the presence of normal sensory or direct visual feedback. The finding of bidirectional referred sensations is particularly novel (cases 2 and 3) and would be impossible to demonstrate in amputees (where the condition is clearly irreversible).

Visual feedback strongly influenced the experience of RS. It is difficult to elicit whether this was true in patients who described RS following amputation, as the methodology in previous reports is not explicit. Moreover most, but not all, phantom limb sensations (where upper limbs are concerned) involve the face or torso, which are not directly viewable on stimulation. Touch and vision are inextricably linked. Touch is known to influence vision, such as dispelling the visual illusion of a three-dimensional object when it is drawn on a flat surface. Equally, in some clinical conditions such as somatosensory

loss after stroke, visual feedback of the affected limb during testing can significantly improve reported perception [27]. In addition, recent findings by Taylor-Clark *et al.* [28] showed that the enhancing effect of vision modulated somatosensory cortical processing. Gregory [29] points out that vision evolved from the simpler processes for touch and that it is possible the somatosensory map is inverted (the feet above the hand) in order to correspond with the inverted visual image on the retina. This ensures that the link between vision and touch is as short as possible. Consequently, when our subjects viewed their limbs being stimulated it would appear that the more powerful sense of vision overruled the referred sensations.

The incidence of referred sensations in CRPS was previously unknown, but in this cross-sectional study they were shown to be present in approximately a third of the total study population. Further work, on larger populations, is now required to try to identify any factors that may contribute to the existence of referred sensations and whether their presence is significant to the course of the individual's disease.

In conclusion, the existence of referred sensations in patients with CRPS type 1 provides evidence of associated central sensory plasticity resulting in or from impairment to peripheral neural systems.

### Conflict of interest

The authors have declared no conflicts of interest.

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# **Appendix 9**

# A controlled pilot study of the utility of mirror visual feedback in the treatment of complex regional pain syndrome (type 1)

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P. D. Wall<sup>2</sup> and D. R. Blake

**Background.** We assessed mirror visual feedback (MVF) to test the hypothesis that incongruence between motor output and sensory input produces complex regional pain syndrome (CRPS) (type 1) pain.

**Methods.** Eight subjects (disease duration  $\geq 3$  weeks to  $\leq 3$  yr) were studied over 6 weeks with assessments including two controls (no device and viewing a non-reflective surface) and the intervention (MVF). Pain severity and vasomotor changes were recorded.

**Results.** The control stages had no analgesic effect. MVF in early CRPS ( $\leq 8$  weeks) had an immediate analgesic effect and in intermediate disease ( $\leq 1$  yr) led to a reduction in stiffness. At 6 weeks, normalization of function and thermal differences had occurred (early and intermediate disease). No change was found in chronic CRPS.

**Conclusions.** In early CRPS (type 1), visual input from a moving, unaffected limb re-establishes the pain-free relationship between sensory feedback and motor execution. Trophic changes and a less plastic neural pathway preclude this in chronic disease.

**KEY WORDS:** Complex regional pain syndrome, Mirror visual feedback.

Complex regional pain syndrome (CRPS) is a painful, debilitating condition. This diagnostic term embraces several syndromes, including reflex sympathetic dystrophy, causalgia and algodystrophy. Characteristic clinical features include sensory disturbances, such as burning pain with allodynia and hyperalgesia; motor disturbances, such as weakness, tremor and muscle spasms; and changes in vascular tone, temperature and oedema [1]. Over time, functional loss and trophic changes may occur. The syndrome can occur spontaneously or following trauma (CRPS type 1) or in association with peripheral nerve damage (CRPS type 2). This paper addresses patients presenting with CRPS type 1.

A characteristic feature of CRPS is that signs and symptoms spread beyond the site of initial insult. Severe pain may occur seemingly out of proportion to the original pathology. It may persist over long periods and

is frequently resistant to a wide range of treatments. Traditionally, interrupting the sympathetic supply to the painful area was thought to treat such pain. However, the effectiveness of this approach is not supported by randomized controlled trials [2]. Recent studies on other intractable pain conditions have reported the analgesic benefits of mirror visual feedback therapy [3]. Phantom limb pain, relieved by this therapy, has many characteristics similar to CRPS pain (burning, cramping, and mislocalized). We therefore investigated the effect of mirror visual feedback in CRPS.

The classical picture of a pain mechanism as a single hard-wired, dedicated pathway is no longer widely held [4, 5]. Instead, converging evidence from physiological and functional imaging studies suggests a much more diffuse and plastic system involving the cord, brainstem, thalamus and cortex [6]. In addition, psychological

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states such as attention, anticipation and preparation for action may be inherent, essential components modulating the experience of pain. Abnormal plastic changes in the CNS have been associated with a number of pain syndromes [7, 8] including phantom limb pain [9]. For example, using non-invasive neuromagnetic imaging, Flor *et al.* [10] found a strong relationship between the amount of plastic change in primary somatosensory cortex and the extent of phantom pain experienced.

Ramachandran and Roger-Ramachandran [3] proposed that phantom limb pain results from disruption of the normal interaction between motor intention to move the limb and the absence of appropriate sensory (proprioceptive) feedback. They speculated that visual feedback might interrupt this pathological cycle. Using a mirror that enabled amputees to superimpose the visual image of their normal limb on the location where they felt their phantom limb to exist, Ramachandran and Roger-Ramachandran [3] found that the phantom spasms and their associated pain were rapidly relieved during exercises involving the 'virtual limb' in six out of 12 cases. Harris subsequently hypothesized, on the basis of clinical observation and functional imaging studies [11], that disorganized cortical representations may lead to the experience of peripheral pain. He proposed that a mismatch between motor intention and predicted proprioceptive or visual feedback of the affected limb may drive this process [12].

We hypothesized that the pain of CRPS is a consequence of disruption of central sensory processing and that congruent visual feedback from the moving unaffected limb, as provided by a mirror, would restore the integrity of cortical processing, thereby relieving pain and restoring function in the affected limb.

## Method

### Participants

Adult subjects who conformed to the diagnostic criteria for CRPS type 1 [1] in a single limb were recruited consecutively from the out-patient clinics at the Royal National Hospital for Rheumatic Diseases, Bath over an 18-month period. We excluded patients with CRPS type 2, for example those with peripheral nerve lesions.

### Clinical method

Subjects were assessed at two time points: on presentation and 6 weeks later. The assessment protocol was divided into three distinct stages: two control phases (using no device and viewing a non-reflective surface) and an intervention phase (viewing a mirror). An additional daily diary was used to record frequency of mirror use and pain severity between assessments. Visual analogue scales (VAS) were used to assess pain intensity, with 0=no pain and 10=pain as bad as it could be. Infrared thermography (IRT) was used to quantify vasomotor changes that influenced temperature in the affected and unaffected limbs [13]. Images were taken on presentation and at week 6.

Subjects were seated and initially asked to visualize both limbs (affected and unaffected). Pain at rest and on movement was recorded (control phase 1). A non-reflective board was

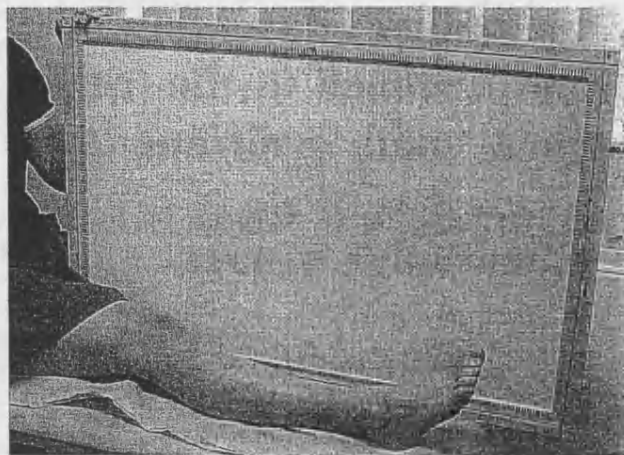


FIG. 1. Subject viewing non-reflective surface with painful limb hidden.

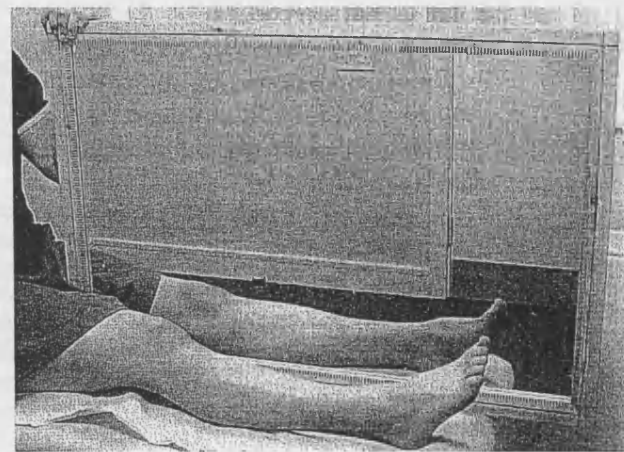


FIG. 2. Subject viewing non-painful limb in mirror with painful limb hidden.

then positioned perpendicular to the subject's midline, with the unaffected limb facing the non-reflective surface and the affected limb hidden (control phase 2). Subjects were asked to attend to the non-reflective surface for a period of 5 min and exercise their non-painful limb and, if possible, their painful limb in a congruent manner (Fig. 1). All subjects were asked to attempt to perform similar exercises: flexion-extension cycles of the relevant body parts. The range of movement and speed of these exercises was dictated by the subject's pain. Following the control stages, a mirror of similar size to the control device was positioned so that only the unaffected limb, and its reflected image in the mirror, could now be seen (Fig. 2). Subjects attended to the reflection now occupying the space of their painful limb. Again, subjects were requested to exercise both limbs (flexion-extension cycles as described above) for 5 min in a congruent manner. Pain on movement was recorded after each control and intervention stage.

Following the initial procedures, subjects were directed to use the mirror as frequently as they wished. A maximum time limit of 10 min was set for each period of mirror therapy to ensure concentration was maintained. Subjects were also advised to conduct the treatment protocol in a quiet environment, where



concentration would not be interrupted. Subjects recorded daily the frequency of mirror use and their movement-related pain score.

## Results

(Table 1) Eight subjects were recruited, aged 24–40 yr (mean 33 yr) with disease duration of 3 weeks to 3 yr. Three subjects had early disease ( $\leq 8$  weeks), two had disease of intermediate duration (5 months and 1 yr) and the remaining three had long-standing disease ( $\geq 2$  yr). CRPS was precipitated by trauma in four of the eight subjects (cases 3, 5, 7 and 8); no obvious precipitant was identified in the remaining four. Case 6 had a concurrent diagnosis of ankylosing spondylitis but there was no clinical or imaging evidence of synovitis or enthesopathy in the painful region. Case 7 had extensive ulcers on the affected limb and all three chronic cases (cases 6–8) had contracture deformities in the CRPS-affected limb due to prolonged immobility.

All presented with a single limb affected by allodynia, hyperalgesia, reduced movement with related pain and stiffness and vasomotor disturbances. The only exception to this was case 4, who reported severe stiffness of the limb with little pain on movement but met all other criteria.

All subjects had had previous interventions that did not relieve pain, including analgesia, physiotherapy modalities, sympathetic blocks, immobilization, transcutaneous electrical nerve stimulation, osteopathy and acupuncture (Table 2). The more chronic cases had received the greater number of interventions, which included sympathetic blocks and immobilization. Standard physiotherapy treatment was continued throughout the study period (Table 3) for all subjects except case 5, who had discontinued treatment prior to the start of the study due to lack of benefit. The analgesic type, dose and frequency remained constant during the pre-study period and throughout the study period for those with chronic disease (cases 6–8). However, cases 1–5 reduced their analgesic requirements as the study progressed and at the 6-week follow up only case 5 still required any form of analgesia, and this only intermittently.

### Control stages

All subjects reported no relief of pain on movement when both limbs were visualized without a device or when the non-reflective surface was viewed. Indeed, movement exacerbated pain. Control phase 2 of the protocol (using a whiteboard in place of the mirror) was only performed at the initial assessment. The reason for this was that the participants who experienced an immediate analgesic response with the mirror were aware that the whiteboard trials were purely for control purposes. It therefore no longer worked as a fair control, and as the mirror was so clearly beneficial to these participants they were reluctant to continue with the whiteboard. In order to keep the protocol uniform across the study participants, this phase was dropped for the 6-week intervention stage.

TABLE 1. Patient characteristics and the effect of the control and intervention phases on their pain at presentation; the frequency of mirror use on follow-up and final pain scores at 6 weeks with infra-red thermal temperature differences between affected and unaffected limbs

Subject, painful limb, age (yr), sex	Symptom duration	At presentation			Follow-up									
					Frequency of mirror use (times per day) (duration of each treatment 10 min)									
					Week									
					1	2	3	4	5	6	Pain VAS	Mean temp. diff. (°C)	Treatment duration (weeks)	
1. LL, 38, F	6 weeks	Pain VAS at rest	Pain VAS on movement	Intervention <sup>d</sup> Pain VAS on movement	8	3	3	3	2	0	0	0.2	6	
2. LA, 28, F	3 weeks	9	9	2	4	4	3	3	2	0	0	0.4	6	
3. LL, 34, F	8 weeks	6	8	3	9	4	3	0	0	0	0	0.8	4	
4. RA, 35, F	5 months	0	5 <sup>e</sup>	3 <sup>e</sup>	5	4	5	4	5	4	2 <sup>e</sup>	0.3	6	
5. RA, 40, M	1 yr	4	6	6	5	4	5	4	4	3	1	0.4	6	
6. LL, 24, M	2 yr	7	8	8	5	5	5	0	0	0	8	1.3	Unresolved	
7. LL, 38, F	3 yr	4	5	5	4	4	0	0	0	0	5	n.d.	Unresolved	
8. LL, 27, M	2 yr	7	8	8	4	4	0	0	0	0	8	2.6	Unresolved	

LA, left arm; LL, left leg; RA, right arm; F, female; M, male; n.d., not done.

<sup>a</sup>Region of interest constant significant difference if  $>0.4^{\circ}\text{C}$ ; <sup>b</sup>both limbs (no device); <sup>c</sup>painful limb hidden; <sup>d</sup>mirror visual feedback; <sup>e</sup>stiffness; <sup>f</sup>case 7 had widespread ulceration on her left leg, which made thermal imaging impossible.



TABLE 2. Therapeutic interventions before mirror visual feedback

Subject	Analgesia	IRSB (G)	Physiotherapy modalities	Occupational therapy	Immobilization	TENS	Osteopathy	Acupuncture
1	NSAID, simple		+					
2	NSAID, compound		+	+				
3	Compound		+					
4	NSAID		+				+	
5	Compound		+		+			
6	Opioid	+	+					+
7	Opioid	+	+		+	+		
8	NSAID	+	+		+			

IRSB (G), intravenous regional sympathetic blockade (guanethidine); TENS, transcutaneous electrical nerve stimulation; NSAID, non-steroidal anti-inflammatory drug.

### Intervention stage

All three subjects with early CRPS ( $\leq 8$  weeks) reported a striking reduction in their pain VAS during and after visual feedback of their moving, unaffected limb as provided by the mirror. A marked analgesic effect was observed within a few minutes of mirror use, followed by an abrupt return of pain when the mirror was removed initially. With repeated use (four to nine times daily, week 1), the period of analgesia extended progressively from a few minutes to hours, requiring less mirror use over the 6-week study period. At 6 weeks there was a reversal of vasomotor changes as measured by IRT, a return to normal function and no pain at rest or on movement. All three subjects felt they no longer required analgesic relief from the mirror and had stopped prior to assessment at 6 weeks (case 3, week 4; cases 1 and 2, week 6).

The two subjects with intermediate disease duration (5 months and 1 year; cases 4 and 5) reported that the mirror immediately eased their movement-related stiffness but there was no analgesic effect in case 5. They both reported that this reduction in stiffness facilitated movement and the effect lasted for increasing periods after use of the mirror. Although no objective data were collected on function, both subjects felt that by 6 weeks function had improved to such an extent that they were able to return to their usual manual occupations. Interestingly, despite the lack of analgesic effect during the mirror visual feedback procedure, case 5 reported reduced pain at the 6-week follow-up (VAS 6/10 at presentation and 1/10 at 6 weeks). Reversal of IRT temperature differences was recorded in case 4 at 6 weeks, and case 5 remained with no significant difference between the two affected limbs.

No subjective relief of pain and stiffness or reversal of IRT temperature differences was observed in the three subjects with chronic disease ( $\geq 2$  yr) and they had all discontinued mirror use by the end of week 3 due to lack of effect.

### Comment

Our observations, the first of their kind in CRPS, suggest that congruent visual feedback of the moving unaffected

TABLE 3. Treatment received during study protocol in addition to mirror visual feedback

Subject	Analgesia	Physiotherapy modalities	Occupational therapy	Osteopathy
1	Simple	+		
2	NSAID	+	+	
3	Compound	+		
4	None	+		+
5	Compound			
6	Opioid	+		
7	Opioid	+		
8	NSAID	+		

NSAID, non-steroidal anti-inflammatory drug.

limb, via a mirror, significantly reduces the perception of pain in early CRPS (type 1) and stiffness in the intermediate stages of the disease. The extent of the analgesic effect surprised both patients and investigators. The abrupt return of pain and stiffness when the mirror was removed supports the view that we were reliably able to influence these sensations. The two internal control stages excluded an analgesic effect from (i) moving the affected limb with normal visual feedback alone and (ii) the influence of selective attention when the limb was hidden. A placebo response is therefore highly unlikely, given the above control stages and the lack of benefit in chronic CRPS subjects. The effect was consistent between the five less chronic subjects and repeatable within subjects. Extended use of the mirror provided increasing periods of analgesia, which aided compliance with exercise regimens. Whilst early CRPS can resolve spontaneously, we are unaware of any therapeutic manoeuvres or drug effects that can achieve such an immediate analgesic effect. In addition, when the intervention is stopped there is an abrupt return of pain. Mirror visual feedback is a simple, inexpensive and, most importantly, a patient-directed treatment.

Our results support the hypothesis that the CNS is capable of generating a feedback-dependent state that can produce pathological levels of pain. In CRPS, this might involve a mismatch between different interdependent modalities, such as a disruption of normal interaction between motor intention and sensory feedback. In those

with inherent vulnerability to this incongruence it can lead, in some, to referred, intractable pain following trauma, and in others it can promote CRPS with a CNS origin. This might explain why some types of CRPS occur without discrete peripheral injury.

Our subjects' pain and stiffness, signalled by this incongruence, can be corrected by the use of false but nevertheless congruent visual feedback of the unaffected limb. The mirror reflection permits the subject to rehearse and practice movements of the affected limb without having to directly activate those parts of maladaptive central processes that typically produce pain. The centrally processed visual input, which appears to originate from the dysfunctional and painful side, acts to re-establish the normal pain-free relationship between sensory feedback and motor intention and consequently results in the rapid resolution of the pain state. In the absence of mirror feedback, movement exacerbates the pain, as was demonstrated in our control stages. In our subjects with long-standing disease there are two possible reasons why mirror visual feedback was ineffective. The first was that trophic changes, such as contractures, limited movement, and the second was that neural pathways may be more established over time. The effect in the two intermediate cases, in whom the easing of stiffness was more apparent than an analgesic response, provides further evidence that time plays a part in this process. Interestingly, single photon emission computed tomography studies [14] have shown that the early stages of the illness are associated with increased blood flow in the thalamus while in the later stages this region shows hypoperfusion. These changes and the peripheral changes that occur over time may explain the lack of treatment effect in subjects with chronic CRPS and the more limited effect in the intermediate cases.

Notwithstanding the therapeutic implications, our results provide an important insight into the pathogenesis of CRPS and possibly other conditions presenting with 'inappropriate' pain. Larger studies, supported ideally by functional imaging, are required.

During the final preparation of this manuscript, Professor Patrick Wall died (8 August 2001) and the other authors would like to dedicate this paper to his memory.

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# **Appendix 10**

# Phantoms in rheumatology

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**Abstract.** This paper examines rheumatology pain and how it may relate to amputee phantom limb pain (PLP), specifically as experienced in rheumatoid arthritis, fibromyalgia and complex regional pain syndrome (CRPS). Clinical findings, which suggest cortical sensory reorganization, are discussed and illustrated for each condition. It is proposed that this sensory reorganization generates pain and altered body image in rheumatology patients in the same manner as has previously been hypothesized for amputees with PLP; that is via a motor/sensory conflict. The correction of this conflict through the provision of appropriate visual sensory input, using a mirror, is tested in a population of patients with CRPS. Its analgesic efficacy is assessed in those with acute, intermediate and chronic disease. Finally, the hypothesis is taken to its natural conclusion whereby motor/sensory conflict is artificially generated in healthy volunteers and chronic pain patients to establish whether sensory disturbances can be created where no pain symptoms exists and exacerbated when it is already present. The findings of our studies support the hypothesis that a mismatch between motor output and sensory input creates sensory disturbances, including pain, in rheumatology patients and healthy volunteers. We propose the term *ominory* to describe the central monitoring mechanism and the resultant sensory disturbances as a *dissensory* state.

*2004 Osteoarthritic joint pain. Wiley, Chichester (Novartis Foundation Symposium 260) p 154–178*

Pain is the predominant complaint of patients with a rheumatological condition. It may be intermittent or continuous and vary in nature depending on the cause and course of the disease. In the majority of cases clinical findings provide supporting evidence for the source of this pain such as swollen joints in rheumatoid arthritis (RA) or bony overgrowth in osteoarthritis (OA). However, there are some conditions in rheumatology where a patient's pain cannot be matched to physical findings or relieved by traditional therapeutic measures. It is pain of this nature that this paper addresses, specifically the types of pain experienced in rheumatoid

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<sup>1</sup>This paper was presented at the symposium by D. R. Blake to whom correspondence should be addressed.

arthritis (RA), fibromyalgia and complex regional pain syndrome (CRPS), and how these may relate to amputee phantom limb pain.

### **Amputee phantom limb pain**

Phantom limb pain (PLP) is a phenomenon that occurs in approximately 70% of patients after amputation (Jensen et al 1985). For the amputee 'these pain memories are vivid, perceptually integrated experiences which incorporate both emotional and sensory aspects of the pre-amputation pain' (Hill et al 1996). Tingling is the most common complaint but pins and needles, shooting, burning or crushing pain have all been reported (Melzack 1971). Phantom sensations are also described by 90–100% of amputees (Melzack 1990). Post-operatively an amputee will perceive a phantom limb that has all the same sensations and mobility of the real limb prior to amputation and is so strikingly real to the individual that it feels an integral part of them. The phantom appears to 'inhabit the body' (Melzack 1990) when the eyes are open and moves appropriately with other limbs. It initially feels perfectly normal in size and shape but may alter over time so that the phantom gradually becomes less apparent and may eventually fade away (Katz & Melzack 1990). For those people who wear a prosthesis the phantom limb can appear to fill it or telescope up into the remaining stump (Melzack 1990). It has been proposed that it is a combination of the duration and intensity of such pre-operative pain that determines whether long-term central nervous system processes are altered with resulting persistent phantom sensations (Katz & Melzack 1990). A long-lasting mild sensation such as a watch on a wrist or a sock on a foot may be just as effective at developing somatosensory memories as the intense short-term pain of gangrene.

Referred sensations (RS) have also been described in amputees. These are somatosensory feelings that are perceived to emanate from a body part other than but in association with the body part being stimulated. They have not only been reported following limb amputation (Ramachandran et al 1992), but also somatosensory deafferentation (Clarke et al 1996), local anaesthesia (Gandevia & Phegan 1999), stroke (Turton & Butler 2001) and spinal cord injury (Moore et al 2000). Collectively these studies have shown that the referred sites (the body part not physically touched) are non-random and often closely correspond to the cortical topographical map representing the body structure first described by Penfield and Rasmussen (1950). In the case of an amputated upper limb, patients report sensation in their phantom when parts of the face are lightly stroked (Ramachandran et al 1992). This is thought to be because the hand is positioned adjacent to the face on Penfield's map. These aberrant somatosensory, but reliable sensations were interpreted as resulting from central sensory

reorganization following disconnection or dysfunction of sensory pathways (Ramachandran et al 1992).

In conclusion, amputees report a variety of sensations that are not supported by conventional notions of clinical pathology. The nature of the sensations described, provide the first link to the rheumatology patient with unexplained pain.

## **Pain in rheumatology**

### *Rheumatoid arthritis*

Rheumatoid Arthritis (RA) affects one per cent of the population and is a chronic disabling disease which occurs two thirds more frequently in women than men (Walker 1995). The peak age of onset is between 40 and 50 years, its aetiology is uncertain and there is, as yet no cure. The main symptoms of this disease are pain, stiffness, fatigue and joint swelling but other organs in the body may also be involved (Gordon & Hastings 1995). The pain that these patients experience is 'chronic, unpredictable and frequently severe' (Parker et al 1989) and combined with joint destruction results in progressive disability over time.

A key feature of RA is a pattern of remissions and flares that are a result of the fluctuations in disease activity. During these flares the joints, particularly the small joints of the hands and feet, become swollen and tender. This swelling is due to increased activity in the joint caused by an inappropriate inflammatory response. As a result of prolonged or frequent episodes of this inflammation the synovium lining the joint, becomes permanently thickened and bony erosions may occur (Gordon & Hastings 1995).

Pain is synonymous with the disease of rheumatoid arthritis and the types of pain that sufferers of this disease experience are complex and varied. The descriptions that they use may alter depending on the time of day, the duration of their disease, the joints that are involved and whether those joints are moving or at rest (Papageorgiou & Badley 1989).

A less well-reported quality of pain that some RA patients describe is where they feel their joints to be excessively more swollen than they look. They describe all the sensations associated with swollen joints but they are clinically not swollen and indeed when the subject looks at the affected joints they too are aware that they are not swollen (Blake et al 2000). Interestingly this perception of swelling is not isolated to the joints, the patient will report that they feel their whole digit to be affected (Fig. 1). These sensations are similar to the effects you may have after an injection in your mouth at the dentist. The anaesthetic leaves you feeling that your lip is huge and yet you look in the mirror and find that it is actually its normal size.

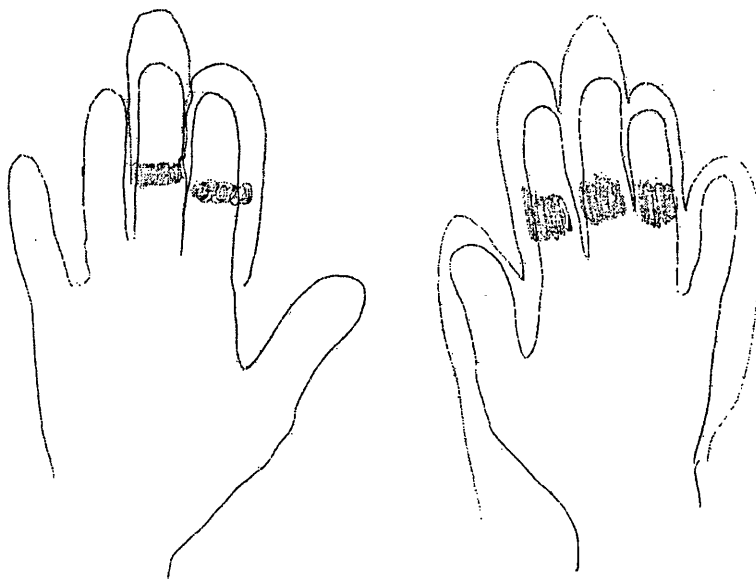


FIG. 1. Rheumatoid arthritis patient's drawing of 'phantom swelling' affecting their hands. The shaded areas depict perceived swelling over the joints and the outer lines, perceived swelling of the digits.

The characteristics of this 'phantom swelling' and how it differs from routine reports of RA joint swelling, were identified in a cross-sectional study involving 10 patients with RA (McCabe 1999). Five of the subjects reported 'phantom swelling' and five did not. The two groups did not differ significantly in age, disease duration or disease activity, as measured by inflammatory markers and joint activity. Using a modified McGill Pain Questionnaire (MPQ), each subject was asked to describe the sensations they currently experienced in all their joints at rest and on movement. A semi-structured interview was used to collect additional information on duration and severity of disease in each joint and the impact of vision on the sensations that they reported.

The subjects with 'phantom swelling' reported that their affected joints felt excessively hot ('burning', 'scalding') and hugely swollen ('massive'). Their remaining RA-affected joints were described in exactly the same manner as the control group described theirs, 'warm' and 'slightly puffy'. When the phantom swollen joints were viewed by the subjects the perception of swelling disappeared but the lesser sensation of 'slight puffiness' in their other joints remained on visualization. Phantom swelling was only present in those joints that had been most severely affected by RA and for the longest duration which

is very reminiscent of Katz and Melzacks' theory that it takes a certain duration and intensity of pain to alter central processing resulting in persistent sensations.

Interestingly the nature and cause of stiffness in RA, another pain related symptom, is not well explained, even though it is a well established and defining symptom of the disease (Arnett 1988). Objective measures of stiffness do not relate to the subjective experience and indeed, compared with non-arthritis controls, objective stiffness can be reduced in RA joints (Helliwell et al 1988). We therefore hypothesised that the central nervous system is capable of generating a feedback-dependent state which can result in pathological sensations such as pain and stiffness in RA, that are to some extent independent of the initial peripheral pathology. We sought clinical evidence to support this proposal by investigating the clinical presentation of perceived stiffness in RA patients who had undergone limb amputation but nevertheless retained an experience of a phantom limb (Haigh et al 2003).

Three patients with a current diagnosis of RA and lower limb amputation were identified from the local Artificial Limb Centre database and investigated to determine the nature and pattern of pain and stiffness in their phantom and intact limb. In addition to standard physical examination, pain and stiffness severity were measured using visual analogue scales (VAS) for both limbs. The duration and timing of stiffness was also recorded for each limb. In all three cases, the pattern of perceived RA stiffness was similar for the intact and phantom limb. All three patients described stiffness in their phantom limb which mirrored that of physical RA joint symptoms in terms of quality, frequency, diurnal variation, location, distribution and response to medication (non-steroidal anti-inflammatory drugs, corticosteroid, opiate and disease-modifying drugs). Unilateral exercise (or attempted exercise) relieved stiffness only in the limb being exercised. Thus, the extent to which the subjective experience of perceived stiffness could be dissociated from the assumed original peripheral source was strikingly illustrated in RA patients with phantom limbs.

Accordingly, we proposed that the experience of peripherally located stiffness results from impairment to central brain processes. Conditions are present in RA to produce inaccurate sensory information which may lead to conflict with planned output from motor systems. These include peripheral and central proprioceptive abnormality, cortical reorganization, neurogenic inflammation and circulating cytokines with central effects. Such conflict of information is ultimately perceived as 'stiffness' by the patient with RA.

RA is not the only rheumatological condition where phantom swelling and stiffness are described. Clinical experience has long shown that patients with fibromyalgia also report stiffness and perceive body areas to be subjectively swollen when objectively they are not.



*Fibromyalgia*

Fibromyalgia (FMS) is a chronic pain condition where sufferers report widespread pain, fatigue and psychological distress all of which have a major impact upon their daily lives (Wolfe et al 1990). Although hyperalgesia and allodynia are commonly reported at specific trigger points these sensations often spread far beyond these areas with sufferers describing generalized sensitivity (Staud et al 2001). For the majority of patients there is no known initiating event or observable physical pathology and symptoms are frequently resistant to therapeutic initiatives.

In addition to the symptoms described above it has long been observed, but only recently systematically recorded, that these patients also experience phantom swelling sensations in the same manner as those with RA (C. McCabe, D. Blake, unpublished work 2001). The sensation most commonly affects the hands, bilaterally from the wrist to the ulna styloid, or the feet, bilaterally from the toes to the ankle joints. The subject is most aware of the perceived swelling when they have their eyes closed and it decreases or disappears completely when they view the affected area. With regular viewing on a daily basis the sensation can be diminished permanently. When phantom swelling is reported it is commonly associated with the patient feeling that they are clumsy or less aware of where their limbs are in space. This reduction in limb position sense will be discussed further towards the end of this paper. Phantom swelling in FMS is a clear example of a sensation being reported without supporting underlying clinical pathology and CRPS is another such condition where the cause of the characteristic symptomology is ambiguous.

*Complex regional pain syndrome*

Complex regional pain syndrome (CRPS) is a painful, debilitating condition. This diagnostic term embraces several syndromes including reflex sympathetic dystrophy, causalgia, and algodystrophy. The pain that a patient with CRPS will report shares many similar characteristics to amputee phantom limb pain: mislocalized, intense and burning. Clinical features include sensory disturbances such as burning pain with allodynia and hyperanalgesia, motor disturbances such as weakness, tremor and muscle spasms, and changes in vascular tone, temperature and oedema (Scadding 1999). Over time functional loss and trophic changes may occur. The syndrome can occur spontaneously or following trauma (CRPS Type 1) or in association with peripheral nerve damage (CRPS Type 2).

A characteristic feature of CRPS is that signs and symptoms spread beyond the site of initial insult. Severe pain may occur seemingly out of proportion to the original pathology. It may persist over long periods and is frequently resistant to a wide range of treatments. Theories abound on the cause of this pain and its

underlying pathology. Traditionally, interrupting the sympathetic supply to the painful area was thought to treat such pain. However, the effectiveness of this approach is not supported by randomised controlled trials (Jadad et al 1995).

Neural plasticity occurs in a variety of pain syndromes (Harris 1999, Lenz & Byl 1999). We predicted that referred sensations would be present in patients with CRPS type 1 as evidence of sensory cortical reorganization. The resultant sensory mislocalizations could then provide the inappropriate sensory feedback required to create painful sensations (McCabe et al 2003a). Furthermore, we hypothesized that these referred sensations would be perceived to emanate from the body structures immediately adjacent to the stimulated site and in keeping with their topographical location on the Penfield homunculus as in phantom and allied pain states. We specifically selected those patients with CRPS Type 1 as we wished to discover whether central reorganization occurs even where there is no evidence of local peripheral nerve damage.

Over two years, 16 subjects (13 female, 3 male) who met the entry criteria were recruited. Five showed evidence of referred sensations (Table 1). There was no difference in age, disease duration, levels of pain, or severity of disease (Table 2) between those who presented with RS and those who did not. All five patients reported referred sensations during examination with their eyes closed (Fig. 2). They were experienced in real time and disappeared when stimulation ceased or vision was permitted. When the subjects viewed the area being touched the sensations were either diminished (Case 5) or not present and when the symptoms of CRPS resolved (Cases 1, 2 and 4), referred sensations were lost. Sensations were referred in a modality-specific manner with touch referred in all cases and pinprick also referred in two (Cases 1 and 2). Vibration was never referred. All referred sites were located on body parts immediately adjacent, on Penfield's homunculus, to the stimulated site.

The location of the referred sites, in our study population, was consistent with previous reports in other pain conditions (Ramachandran et al 1992, Flor et al 1997) and fit particularly well with predicted cortical changes that have been shown to occur within the somatosensory body map in amputees (Halligan et al 1993). Ramachandran (Ramachandran & Hirstein 1998) proposed that due to the location and speed with which referred sensations occur in amputees, such 'ectopic representations' following functional remapping were probably due to the unmasking of latent synapses within the cortex, as previously described in primates (DeFelipe et al 1986, Jones 1990). These synapses are suppressed when there is simultaneous input from two connected receptors but with reduced or impaired sensory activation in one area, the connection becomes disinhibited. Recent imaging studies, using magnetoencephalography, in six patients with upper limb CRPS Type 1 have also shown changes in the cortical somatosensory map though it was not reported whether these were associated with referred

**TABLE 1** Location, direction and type of sensations referred in subjects with a diagnosis of CRPS Type 1 (Cases 1–5). Loss of detection of referred sensations is shown in relation to current disease duration and future status (resolved or chronic)

<i>Patient</i>	<i>Pain site</i>	<i>Disease duration</i>	<i>Area touched (1) Referral site (2,3)</i>	<i>Direction of referral</i>	<i>Type of sensation</i>	<i>Loss of referred sensation</i>	<i>Resolution of CRPS (wks)</i>
Case 1 28 years F (Fig. 1)	Left hand	3 weeks	L 3rd fingertip (1) L lower jaw (2)	1–2	Light touch and pinprick	3 weeks	6
Case 2 34 years F (Fig. 2)	Left ankle	8 weeks	L forefoot (1) L patella (2)	1–2 and 2–1	Light touch and pinprick	3 weeks	4
Case 3 24 years M (Fig. 3)	Left knee	3 years	L patella (1) L forefoot (2)	1–2 and 2–1	Light touch	No	Chronic
Case 4 41 years F (Fig. 4)	Right foot	6 years	R forefoot (1) R patella (2)	2–1	Light touch	4 weeks	Chronic
Case 5 57 years F (Fig. 5)	Left hand	4 years	L shoulder (1) L ear (2) L hand (3)	1–2 1–3	Pulling, light touch and hand movement	No change	Chronic
(Fig. 6)			L cheek (1) L hand (2)	1–2	Light touch		

sensations (Jouttonen et al 2002). There was a significantly shorter distance between the areas representing the thumb and little finger on the somatosensory cortex contralateral to the affected limb than the ipsilateral side. Interestingly, there was no significant correlation between the distance of thumb and finger and the level or duration of pain. Hand dominance was also not an influencing factor.

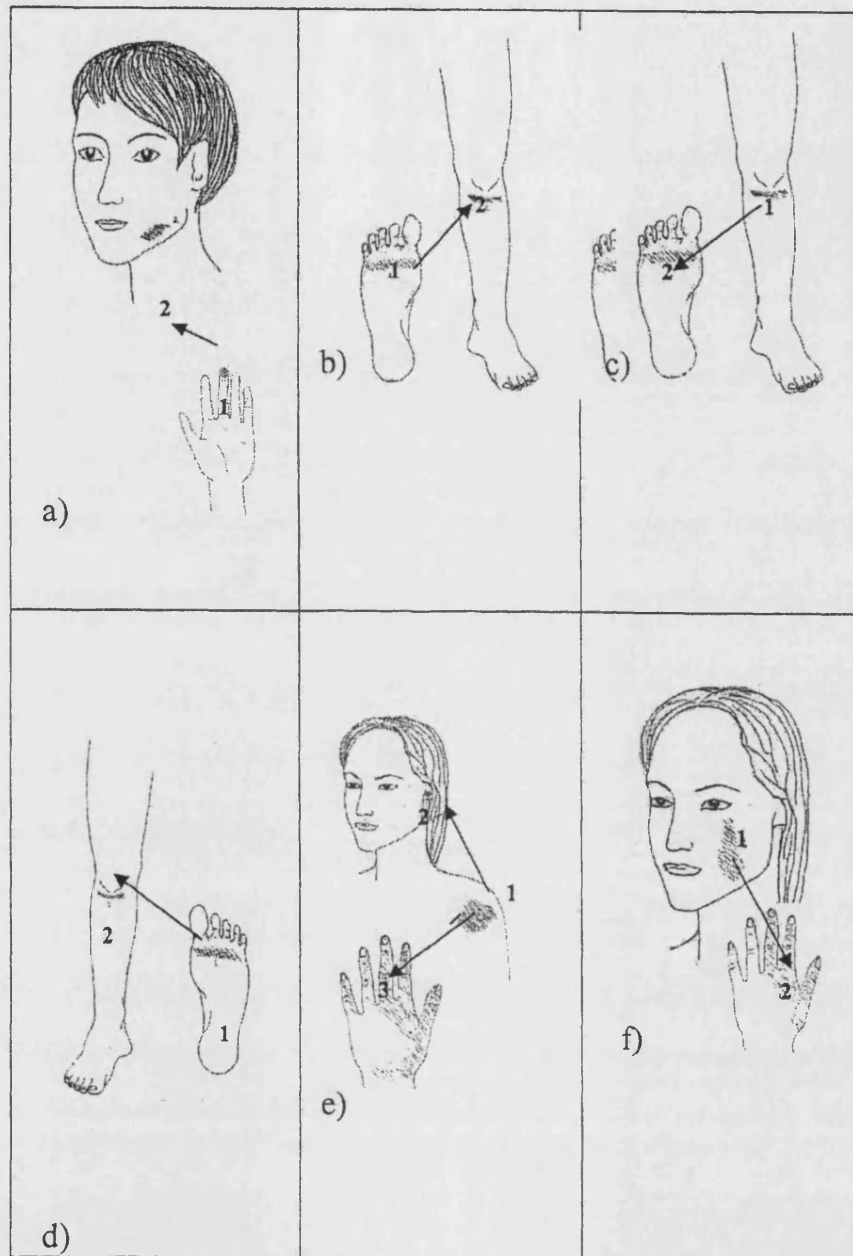
Alternatively, referral of sensations may occur at the spinal level. A large body of evidence shows that sensitization of wide dynamic range neurons at level V of the dorsal horn results in ipsilateral and contralateral enlarged receptive fields which do not rely on a cortical homunculus (Ji & Woolf 2001). In addition, experimental models of peripheral neuropathic pain demonstrate bilateral spinal cord changes after unilateral nerve damage (Koltzenberg et al 1999). However, all of our patients had CRPS 1, so therefore had no precipitating neural trauma. Their sensations were not referred bilaterally, either from the stimulated site to its

**TABLE 2** Demographics of total study population to compare differences in age, disease duration and levels of pain between subjects who experienced referred sensations and those who did not

<i>Case</i>	<i>Age</i>	<i>Gender</i>	<i>Disease duration</i>	<i>Affected limb</i>	<i>Pain level on movement at presentation</i>
1**	28 years	F	3 weeks	Left hand	8
2**	34 years	F	8 weeks	Left ankle	8
3**	24 years	M	3 years	Left knee	8
4**	41 years	F	6 years	Right foot	9
5**	57 years	F	4 years	Left hand	5
<b>Mean**</b>	<b>36.8 years</b>	<b>4F:1M</b>	<b>2.6 years</b>		<b>7.6</b>
6	38 years	F	6 weeks	Left ankle	9
7	35 years	F	5 months	Right arm	5
8	40 years	F	1 year	Right arm	6
9	38 years	F	3 years	Left leg	5
10	27 years	M	2 years	Left leg	8
11	51 years	F	2 years	Right arm	7.5
12	68 years	F	1 year	Left arm	5
13	54 years	M	4 years	Left foot	9
14	38 years	F	7 years	Left foot	10
15	22 years	F	4 years	Left foot	9
16	59 years	F	10 years	Left foot	9.5
<b>Mean</b>	<b>42.7 years</b>	<b>9F:2M</b>	<b>3.1 years</b>		<b>8</b>

contralateral partner (i.e. left hand to right hand) or mirrored on the contralateral side (i.e. from stimulated site to referral site on the unaffected limb). In addition, the speed of referral (both in terms of disease duration, response time on stimulation and resolution as the condition improved), combined with the magnitude of the sensations all detract from a purely spinal route. Contemporary theories suggest that CRPS is a disorder involving both CNS and peripheral nervous system components (Baron et al 2002, Janig & Baron 2002). This is based on the

FIG. 2. Artists impression of Cases 1–5 illustrating location of stimulus and direction of referred sensations (area touched=1, referred site/s=2, 3). (a) to (d) correspond to Cases 1 to 4, (e) & (f) correspond to Case 5. Shaded area (1) depicts area stimulated by examiner, shaded areas (2) & (3) depict where referred sensation were felt. The arrows illustrate direction of referral. Reprinted with permission from McCabe et al (2003d).



evidence that some patients respond positively to sympathetic blockade, thereby implicating involvement of the sympathetic nervous system but conversely, sympathetically maintained pain involves the deep somatic tissue (as demonstrated by our patients' report of increased pain on movement) which is the domain of the autonomic system. Therefore isolating one clear route for referred sensations is at present problematic.

### **The power of vision and mirror visual feedback**

Visual feedback strongly influences the experience of referred sensations in patients with CRPS. Recent studies have shown this also to be the case in amputees where stimulation of the intact limb evoked sensory changes in the phantom only when the subjects' eyes were closed (Hunter et al 2003). Touch and vision are inextricably linked. Touch is known to influence vision such as dispelling the visual illusion of a three-dimensional object when it is drawn on a flat surface. Equally, in some clinical conditions such as somatosensory loss after stroke, visual feedback of the affected limb during testing can significantly improve reported perception (Halligan et al 1997). In addition, recent findings by Taylor-Clarke et al (2002) showed that the enhancing effect of vision modulated somatosensory cortical processing. Gregory (1998) points out that vision evolved from the simpler processes for touch and that it is possible the somatosensory map is inverted (the feet above the hand) in order to correspond with the inverted visual image on the retina. This ensures that the link between vision and touch is as short as possible. Consequently, when our subjects viewed their limbs being stimulated it would appear that the more powerful sense of vision over ruled the referred sensations.

It has already been stated that vision is able to dismiss the sensation of phantom swelling in RA and FMS but in recent studies on PLP vision has been shown to also provide an analgesic benefit. Ramachandran & Rogers-Ramachandran (1996) superimposed the image of amputees' normal limbs, by means of a mirror, on the space that their phantom limbs occupied. Viewing the mirror image of their residual limb, the amputees moved their normal limbs and attempted to move their abnormal side. Subjects reported that sensation in their abnormal limb returned towards normal during the exercises and their pain diminished. Harris (2000) subsequently hypothesized that the reason for this analgesic effect was that PLP is generated by a discordance in motor intention and predicted proprioceptive feedback and that when this mismatch is corrected, through appropriate visual feedback via the mirror, pain is relieved.

Objective evidence of the cortical effects of this mismatch was provided by Fink and colleagues (Fink et al 1999) using PET imaging and healthy volunteers. They demonstrated that when congruent and incongruent movements were performed, whilst viewing only one limb in a mirror, cortical activity varied depending on the

movement. When the limbs moved incongruently and yet were seen, by means of mirror imaging, to move congruently, cortical activity was unilateral, unlike visually observed congruent and actual congruent movement, where bilateral cortical activity was produced. When unilateral cortical activity occurred it was in the right dorsolateral pre-frontal cortex and it was this area that Fink and colleagues concluded was specifically involved in the monitoring of conflict between motor intention and its sensory/perceptual consequences.

The existence of referred sensations in CRPS and evidence of changes in cortical representation (Juottonen et al 2002) suggest that pain in CRPS may also be driven by a mismatch between motor output and sensory input as Harris proposed for PLP. We hypothesized that if this were the case then the provision of appropriate sensory input should correct the mismatch and reduce pain. Modifying Ramachandran's methodology for the relief of PLP, we too used a mirror to provide congruent visual feedback, from the moving unaffected limb, to restore the integrity of cortical processing aiming to relieve pain and restore function in the affected limb (McCabe et al 2003a).

Eight subjects were recruited aged 24–40 years (mean 33 years) with disease duration of 3 weeks to 3 years (three subjects early disease  $\leq 8$  weeks, two intermediate, 5 months and 1 year and the remaining three long standing disease of  $\geq 2$  years). All presented with a single limb affected by allodynia, hyperalgesia, reduced movement with related pain and stiffness, and vasomotor disturbances (Table 3).

All subjects reported no relief of pain on movement when both limbs were visualized without a device or when a non-reflective surface was viewed (Fig. 3). Indeed, movement exacerbated pain. All three subjects with early CRPS ( $\leq 8$  weeks) reported a striking reduction in their VAS for pain, during and after visual feedback of their reflected moving, unaffected limb as provided by the mirror (Fig. 4). A marked analgesic effect was observed within a few minutes of mirror usage, followed by an abrupt return of pain when the mirror was removed initially. With repeated usage (4–9× daily, week 1), the period of analgesia progressively extended from a few minutes to hours, requiring less mirror use over the six-week study period. At six weeks there was a reversal of vasomotor changes as measured by infrared thermal imaging, a return to normal function and no pain at rest or on movement. All three subjects felt they no longer required analgesic relief from the mirror and had stopped prior to assessment at six weeks (Case 3, week 4, Cases 1 and 2, week 6).

The two subjects with intermediate disease duration, 5 months and 1 year (Cases 4 & 5), reported that the mirror immediately eased their movement related stiffness but there was no analgesic effect in Case 5. They both reported that this reduction in stiffness facilitated movement and the effect lasted for increasing periods after mirror usage. Although no objective data were collected on function, both

**TABLE 3** Patient characteristics and the effect of the control and intervention phases on their pain at presentation; the frequency of mirror use on follow-up and final pain scores at 6 weeks with infra-red thermal differences and unaffected limbs

At presentation			Follow up												
Subject (painful limb)	Symptom duration	*Mean temperature difference (°C) [non-painful- painful limb]	Control Phase 1 Looking at both limbs (No device)		Control Phase 2 Painful limb hidden	Intervention Mirror visual feedback	Frequent mirror usage × per day (Duration of each treatment 10 min)						At 6 weeks		
			Pain VAS at rest	Pain VAS on movement	Pain VAS on movement	Pain VAS on movement	Week						Pain VAS	Mean temperature difference (°C)	Treatment duration (weeks)
							1	2	3	4	5	6			
Case 1 (left leg) 38 years F	6 weeks	1.1	9	9	9	2	8	3	3	3	2	0	0	0.2	6
Case 2 (left arm) 28 years F	3 weeks	2.0	7	8	8	3	4	4	3	3	2	0	0	0.4	6
Case 3 (left leg) 34 years F	8 weeks	2.7	6	8	8	2	9	4	3	0	0	0	0	0.8	4
Case 4 (right arm) 35 years F	5 months	1.9	0	5**	5**	3**	5	4	5	4	5	4	2**	0.3	6
Case 5 (right arm) 40 years F	1 year	0.5	4	6	6	6	5	4	5	4	4	3	1	0.4	6
Case 6 (left leg) 24 years M	2 years	1.4	7	8	8	8	5	5	5	0	0	0	8	1.3	Unresolved
Case 7 (left leg) 38 years F	3 years	Not performed***	4	5	5	5	4	4	0	0	0	0	5	Not performed	Unresolved
Case 8 (left leg) 27 years M	2 years	2.1	7	8	8	8	4	4	0	0	0	0	8	2.6	Unresolved

LA, left arm; LL, left leg; RA, right arm; F, female; M, male; n.d., not done. \*Region of interest constant Significant difference if  $> 0.4^{\circ}\text{C}^{13}$ . \*\* Stiffness. \*\*\*Case 7 had widespread ulceration on her left leg which made thermal image interpretation impossible.



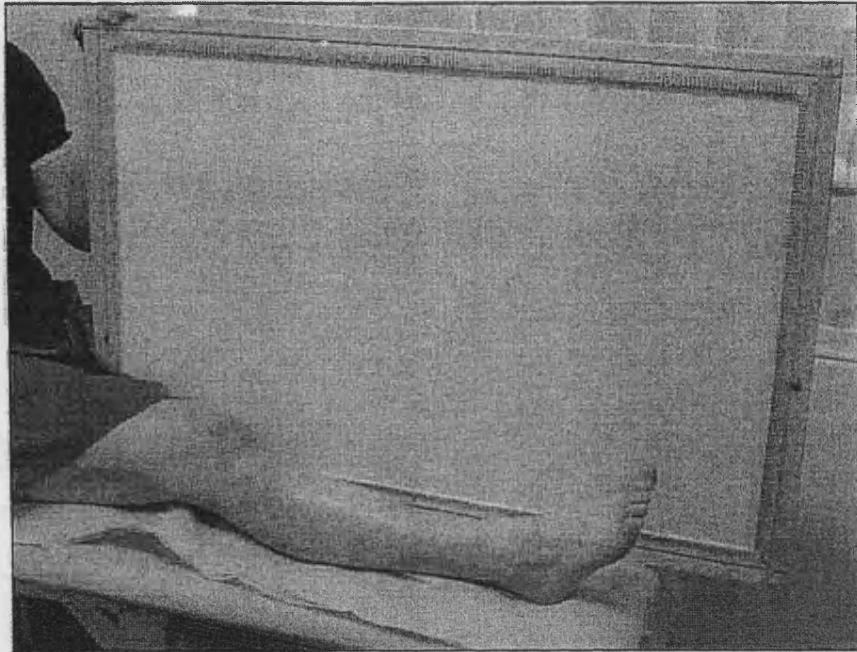


FIG. 3. Subject viewing non-reflective surface with painful limb hidden. Reprinted with permission from McCabe et al (2003a).

subjects felt that by six weeks function had improved to such an extent that they were able to return to their usual manual occupations. Interestingly, despite the lack of analgesic effect during the mirror visual feedback procedure, Case 5 reported reduced pain at the 6 week follow-up (VAS 6/10 at presentation to 1/10 at 6 weeks). Reversal of infrared thermal (IRT) imaging temperature differences were recorded in Case 4 at 6 weeks and Case 5 remained with no significant difference between the two affected limbs.

No subjective relief of pain and stiffness or reversal of IRT temperature differences were observed in the three subjects with chronic disease ( $\geq 2$  years) and they had all discontinued mirror usage by the end of week 3 due to lack of analgesic effect.

These observations suggest that congruent visual feedback of the moving unaffected limb, via a mirror, significantly reduces the perception of pain in early CRPS (Type 1) and stiffness in the intermediate stages of the disease. This supports the hypothesis that the CNS is capable of generating a feedback dependant state that can produce pathological levels of pain. In CRPS, this might involve a mismatch between different interdependent modalities, such as a disruption of normal interaction between motor intention and sensory feedback. In those with

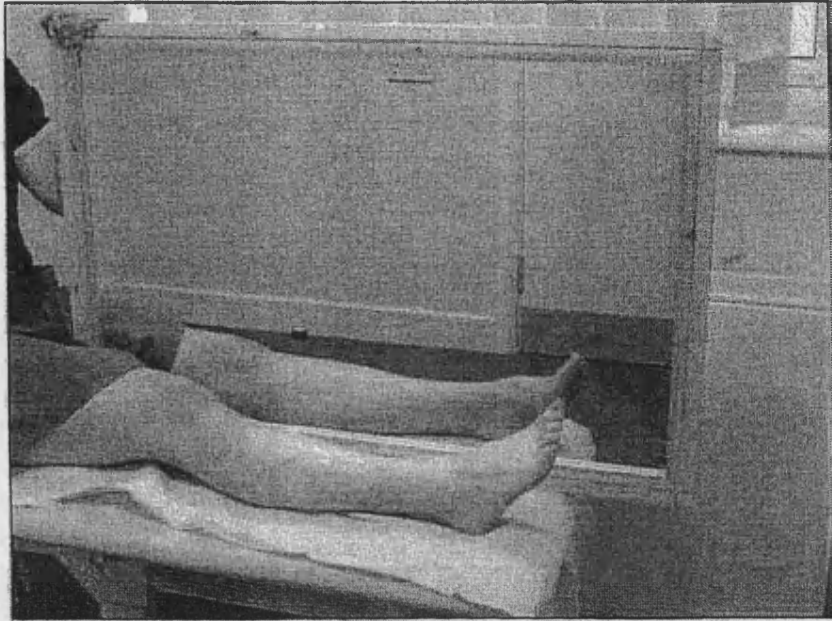


FIG. 4. Subject viewing non-painful limb in mirror with painful limb hidden. Reprinted with permission from McCabe et al (2003a).

an inherent vulnerability to this incongruence it can lead, in some, to referred, intractable pain following trauma or, in others, promote CRPS with a central nervous system origin. This might explain why some types of CRPS occur without discrete peripheral injury.

If the correction of a sensory/motor mismatch produces an analgesic response then the reverse should also be true. That is when expected sensory input is deliberately falsified sensory abnormalities should be generated in healthy volunteers and exacerbated in patients with chronic pain of unknown aetiology.

### Generating pain

In a recent study we invited healthy volunteers and patients with FMS and CRPS to move their upper and lower limbs whilst undergoing normal and altered visual sensory feedback as provided via a mirror (McCabe et al 2003b,c). Motor/sensory conflict was at its optimum when the subjects moved their limbs in opposing directions whilst viewing, via the mirror, their limbs apparently moving together. The primary aim of this study was to comprehensively capture, using a

qualitative methodology, the range of sensory experiences that subjects described as they underwent these manoeuvres. Each assessment was conducted first with the subjects viewing the control side (a whiteboard) and moving their limbs congruently and incongruently and then repeating the movements whilst viewing the intervention side (a mirror).

41 healthy volunteers were recruited (9 males, 32 females) aged 23–65 years (mean 40.4 years). They reported sensory changes at all stages of the protocol, control (congruent movement  $n=6$  [15%], incongruent movement  $n=4$  [10%]) and intervention. However, the maximum number of reports occurred when the subjects moved their limbs incongruently but perceived, via mirror imaging, that they were moving them congruently (congruent movement  $n=10$  [25%], incongruent movement  $n=23$  [56%]). The healthy volunteers reported discomfort ('pins and needles', 'shooting pain'), changes in temperature and/or weight ('floaty sensation' or 'my arm was so heavy I was unable to lift it'), perceived loss of or additional limbs and disorientation ('dizzy', 'strange') (Table 4). Altered sensations were described predominantly in the hidden limb though this sometimes automatically conferred sensations on to the visualized limb, such as a hidden limb felt heavier and therefore the visualised limb was perceived as lighter. All altered sensations faded rapidly after limb movement had ceased and the hidden limb was visualized by the subject.

Data collection in the patient population is still ongoing with 24 patients (7 CRPS Type 1, 17 FMS) recruited to date (3 males, 21 females) aged 23–73 (mean

**TABLE 4** Type and incidence of sensory changes reported by healthy volunteers in hidden limb during congruent and incongruent movement whilst viewing a whiteboard (control) and mirror (intervention)

<i>Type of sensation</i>	<i>Whiteboard congruent movement</i>	<i>Whiteboard incongruent movement</i>	<i>Mirror congruent movement</i>	<i>Mirror incongruent movement</i>
Discomfort/pain	1 (2%)	1 (2%)	4 (10%)	7 (17%)
Temperature change	0	0	0	2 (5%)
Weight change	2 (5%)	0	3 (7%)	6 (15%)
Perceived "loss" of limb	4 (10%)	2 (4.9%)	8 (20%)	11 (27%)
Perceived "extra" limb	0	0	1 (2%)	9 (22%)
Disorientation	3 (7%)	4 (10%)	15 (37%)	13 (32%)
Total number of subjects experiencing any sensory disturbances	6 (15%)	4 (10%)	10 (24%)	23 (56%)

$n=41$  (male=8, female=33).

**TABLE 5** Type and incidence of sensory changes reported by patients with CRPS type 1 and fibromyalgia in hidden limb during congruent and incongruent movement whilst viewing a whiteboard (control) and mirror (intervention)

<i>Type of sensation</i>	<i>Whiteboard congruent movement</i>	<i>Whiteboard incongruent movement</i>	<i>Mirror congruent movement</i>	<i>Mirror incongruent movement</i>
Discomfort/pain	11 (45.8%)	13 (54.1%)	10 (41.6%)	11 (45.8%)
Temperature change	2 (8.3%)	3 (12.5%)	4 (16.6%)	5 (20.8%)
Weight change	7 (29.2%)	8 (33.3%)	5 (20.8%)	10 (41.7%)
Perceived "loss" of limb	5 (20.8%)	8 (33.3%)	13 (54.2%)	14 (58.3%)
Perceived "extra" limb	0	0	0	0
Disorientation	0	6 (25%)	7 (29.2%)	7 (29.2%)
Total number of subjects experiencing any sensory disturbances	20 (83.3%)	15 (62.5%)	15 (62.5%)	16 (66.7%)

*n* = 24 (male = 3, female = 21, fibromyalgia = 17, CRPS = 7).

47.5). Preliminary findings suggest patients perceive the same sensations as the healthy controls but the intensity and frequency of these sensations is greater. For example discomfort is reported as 'crampy', 'sharp' and 'extremely painful', temperature changes as 'very hot', 'burning'. Importantly these sensory changes are described in addition to the subjects current symptoms at all stages of the protocol and for those with CRPS in their affected and unaffected limbs. The other striking difference between the two study populations is that the patients report far more sensory disturbances than the healthy volunteers during the control stages (Table 5). It would appear that when sensory disturbances are already present simply hiding a limb from view is sufficient to exacerbate existing symptoms and generate new ones.

### Summary

Our clinical observations and research studies support the conjecture put forward by Harris (2000) that when motor intentions to move a limb or series of joints no longer matches the corresponding sensory feedback then the subsequent 'misrouting of information' activates a central monitoring mechanism that flags up such incongruity as pain. However, we would now like to extend Harris' theory and propose that this monitoring mechanism is one of many monitoring mechanisms that act as alerts to warn the body that there is a problem with information processing and that pain may be only one of a broad range of sensory disturbances that subsequently occur. These central mechanisms we have

termed ominory from the Latin word *ominor* meaning to prophesy, predict, foreboding. Our studies have focused on the mechanism that monitors motor/sensory conflict but a separate ominory mechanism could generate motion sickness when there is discordance between body position, balance and equilibrium. These mechanisms may be triggered by externally induced conflict (e.g. incongruent movement whilst viewing the mirror) or internally (e.g. disease damage in RA leading to inaccurate execution of movement and/or altered proprioception). The key feature of these mechanisms is that when they are triggered they generate sensory disturbances such as nausea with motion sickness, pain in a phantom limb, phantom swelling and stiffness in RA and FMS. These resultant states we have termed dissensory from the Latin word *dissensio* meaning conflict, disagreement. These are feedback dependent states in that the sensory/motor conflict will continue to trigger the ominory mechanism and ultimately either via duration or intensity of this state the subject will suffer pain. If however, an intervention is targeted to correct the initial source of conflict, the ominory mechanism is suppressed and ideally pain is prevented or alleviated as with mirror visual feedback in early CRPS or the individual visualizing their phantom swollen joints in RA and FMS.

We propose that the threshold at which a person either triggers the ominory mechanism or becomes aware of the subsequent sensory disturbances is individually determined but there will be some who are more sensitive than others. This we assume will relate to the standard variables of genetic factors, age, gender and sex hormone state. This was demonstrated by our healthy volunteer study; not all subjects experienced sensory disturbances. In addition, the preliminary patient data shows that where sensory disturbances are already present a far lower stimulus is required to intensify the problem. Simply hiding a limb from view was sufficient to exacerbate sensory disturbances.

This paper has only addressed three rheumatological conditions, RA, FMS and CRPS, but the same ominory mechanism may apply to the pain of osteoarthritis (OA) and indeed the development of pathological changes in the joint. Sharma et al (1997) and Pai et al (1997) have both shown that patients with unilateral knee OA have worse proprioception in their affected and unaffected joints than elderly controls without OA. The fact that both knees have reduced proprioception even when only one is diseased supports the theory of 'mirror imaging' across the body (Blake et al 2004, this volume). The abnormal proprioception in the contralateral knee will be sufficient to continually trigger the ominory mechanism and perpetuate the problem. The subsequent dissensory state may explain the clinical observation that some individuals report high levels of pain when only minimal changes suggestive of OA are seen on X-ray imaging. This continuous sensory imbalance in the contralateral knee may increase the risk of injury and ultimately of generating OA (Hurley 1997). If targeted exercise is used

to improve proprioception the initial trigger is removed and the ominous mechanism suppressed thereby perhaps preventing the onset of pain. Interestingly, patients with OA often report in clinic that their pain is worse at night and this may be a direct result of reduced corrective sensory input exacerbating the dissensory state. A darkened room diminishes visual feedback and immobilised limbs reduce proprioceptive input.

In conclusion, a mismatch between motor output and sensory input triggers a warning, ominous mechanism in rheumatology patients and healthy volunteers. This generates the dissensory state and the individual will experience sensory disturbances that may include pain.

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# **Appendix 11**

# DISTORTING PROPRIOCEPTION IN FIBROMYALGIA EXACERBATES SENSORY DISTURBANCES-IMPLICATIONS FOR PATHOLOGY.

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**Introduction** Some rheumatology patients report a variety of pains without apparent nociceptive aetiology e.g. Fibromyalgia (FMS) and Complex Regional Pain Syndrome Type 1 (CRPS). It has been hypothesised that discordance between motor intention and sensory perception may generate pain where there is no nociceptive input<sup>1</sup>. When this motor/sensory mismatch is corrected, using a mirror to provide appropriate sensory input, then an analgesic response can be induced as demonstrated in amputees<sup>2</sup> and CRPS<sup>3</sup>. We therefore, hypothesised that the sensations described by our patients with FMS could be exacerbated when the motor/sensory mismatch is increased using false visual feedback.

**Method** 30 subjects  $\geq 18$  years with a diagnosis of FMS conducted a series of bilateral upper and lower limb movements (for a timed 20 second period only) whilst viewing a mirror (M) /whiteboard (W) that created varied degrees of sensory/motor conflict during congruent (Con)/ incongruent (Inc) limb movements. A qualitative methodology captured any changes in sensory experience. The subjects' baseline sensations were recorded initially after 20 seconds of limb movements independent of the equipment.

**Results** Sensory changes were described in addition to the subjects' current symptoms at all stages in the protocol in the subjects' hidden limbs, however the majority of reports were when incongruent visual feedback was induced. (Table 1). Pain ranged from mild to moderate and severe with additional weight change, loss of control of limb, perceived loss of limb and disorientation.

**Table 1**

Percentage of FMS patients reporting additional sensory changes in limbs whilst exercising limbs and viewing whiteboard (control) and mirror. Numbers (%)					
Type of sensation	Baseline	W Con	W Inc	M Con	M Inc
Temperature change	0 (0%)	1 (3%)	1 (3%)	1 (3%)	2 (7%)
Weight change	0 (0%)	4 (13%)	2 (7%)	4 (13%)	9(30%)
Mild Pain	1(3%)	2 (7%)	1 (3%)	1 (3%)	2 (7%)
Moderate Pain	1(3%)	2 (7%)	2 (7%)	2 (7%)	3 (10%)
Severe pain	0 (0%)	2 (7%)	1 (3%)	1 (3%)	1 (3%)
Loss of control of limb	0 (0%)	0 (0%)	0 (0%)	0 (0%)	10 (33%)
Perceived loss of limb	0 (0%)	3 (10%)	4 (13%)	8 (27%)	9 (30%)
Disorientation	0 (0%)	2 (7%)	5 (17%)	6 (20%)	4 (13%)

**Discussion** Our findings support the hypothesis that sensory disturbances can be exacerbated as well as generated in FMS patients when motor output is not matched to expected sensory input. For some, simply obscuring the limb from view is sufficient to generate these sensory disturbances.

**Conclusions** This has important implications relevant to the mechanisms of pain and sensory disturbances in FMS and the tailoring of therapeutic initiatives.

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